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CURRENT CONCEPTS IN CLINICAL NUTRITION

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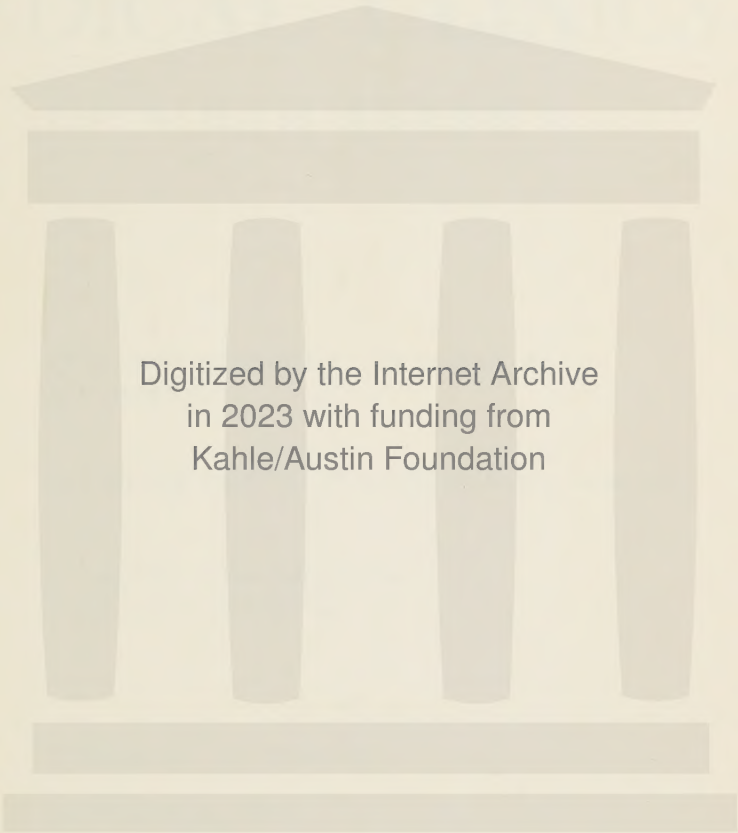
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THE MEDICAL CLINICS OF NORTH AMERICA

CURRENT CONCEPTS IN CLINICAL NUTRITION

SEYMOUR LIONEL HALPERN, M.D., *Guest Editor*

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SYMPOSIUM ON CURRENT CONCEPTS IN CLINICAL NUTRITION

Foreword

SEYMOUR LIONEL HALPERN, M.D., F.A.C.P.

Nutrition plays a ubiquitous role in metabolism, governing many key metabolic pathways and controlling the action of most enzyme systems. It has a pivotal role in maintaining the state of body health at all ages, in determining the rate and extent of growth and development, in affecting the outcome of pregnancy, and in influencing the course and possible complications of disease.

With the rapid advance of therapeutics, nutrition has become one of the most important links in the chain of events which determine whether drug therapy is successful or even needed and which complications from medication will ensue, as well as being a factor in both the prevention and treatment of such complications.

At one time, to most physicians nutrition meant the study of the processes of digestion, absorption, transportation, utilization, and excretion of food. With the discovery of the vitamins and of dietary deficiency diseases, interest in the field of nutrition was stimulated as its catholic function in physiology was recognized. Then an era of complacence evolved in this country as deficiency diseases became increasingly rare. To most physicians nutrition came to denote carbohydrates, proteins, fats, calories, minerals, and vitamins—nothing more.

In the introduction to the September 1964 *Medical Clinics of North America* symposium on Recent Advances in Applied Nutrition, I stated that "a nutrition renaissance" was taking place as the medical profession became more aware of the practical significance of good nutrition in clinical medicine.

A stage in medicine has now been reached which can be called "the era of nutrition." There is good evidence that nutritional disturbances are a significant element in the etiology of such major chronic disorders as atherosclerosis and coronary artery disease. Not only disease processes, but also many physiologic functions such as intellect and learning ability may be influenced by diet.

Nutrition can be defined as that phase of medical science which deals with the study of the effect of food on living organisms and thus of the relationship between man and his food and between diet, health, and disease. Nutrition, food, and health are closely interrelated.

At the present time there is a natural concern for proper nutrition as new methods have been developed to raise the level of health and to alleviate disease through nutrition. There is now a national commitment to a full and healthful diet for every citizen. Nutrition in the 1970's will deal increasingly with such subjects as the role of diet in the cause and treatment of inherited and congenital disorders. It will concern itself more and more with the role of nutrition in longevity and maintaining good health and vigor into old age. Scientists will study the influence of diet on the etiology and course of cardiovascular disorders and cancer, the two leading causes of death in the United States. They will also be concerned with the role of food and diet in arthritis and other prevalent but not fatal chronic diseases.

This "era of nutrition" will find its true place in medical history if the members of the health professions will grasp its significance early in their careers through improved nutrition education in medical schools and in postgraduate study, and if physicians will apply its teachings in their daily practice. Unfortunately nutrition has received inadequate attention in the medical school curriculum and many physicians heretofore have not kept abreast of the rapidly expanding field of nutrition knowledge.

The resurgence of interest in nutrition has resulted in numerous letters being written to the editor of the *Medical Clinics* requesting another issue on recent advances in this subject. Many of the specific areas of nutrition for which more information was requested are covered by the articles in this issue. It does not, however, attempt to be a textbook on nutrition. Some additional articles covering the relationship of nutrition to other organ systems could not be included but will appear in an early issue of the *Medical Clinics*.

The more important areas in which significant progress is being made are reviewed by clinicians recognized to be among the world's leading authorities in their fields. All the articles are current and represent timely information which should aid the physician in the care of his patient and, too, should enlighten him as to present and future nutrition research and the great expectations which can be anticipated therefrom.

SEYMOUR LIONEL HALPERN, M.D., F.A.C.P.
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Diet in Gastrointestinal Diseases

JAMES W. MANIER, M.D.*

Diet has played an important part in the therapy of many gastrointestinal diseases. There is good evidence that dietary manipulation may be of benefit in the management of such less common disorders as gluten enteropathy, specific disaccharidase deficiencies, monosaccharide malabsorption in infants, and galactosemia, as well as in clinical conditions characterized by deficient pancreatic enzymes or bile salts, in which medium chain triglycerides are used. Unfortunately, the significance of diet therapy in some of the more common gastrointestinal disorders, such as peptic ulcer, is not clear. It will, therefore, be the purpose of this paper to review what is and is not known about the dietotherapy of some of these more common gastrointestinal disorders.

ACID PEPTIC DISEASE

Peptic ulcer is one of the most common diseases found in man. For many years its therapy has consisted of the use of a diet composed of "bland" foods, which supposedly stimulates less secretion than other foods and does not physically irritate the ulcer. It has long been observed that pain tends to diminish in patients treated with such a diet. However, it is now well established that ulcer bouts, regardless of treatment, are almost always self-limited. This tends to cast considerable doubt, therefore, on the contention that such diets in themselves are the responsible factor in the healing of the ulcer.

No carefully controlled study of the effects of diet on ulcer healing had been undertaken until 1956, when Doll and co-workers[9] reported their experience with ulcer healing determined by serial radiographs of patients randomly placed on bland or on regular diets. They discovered no difference in the rate of healing between the two groups, except that patients in the hospital, regardless of diet, healed at a more rapid rate than those who were not in the hospital.

Truelove[10] evaluated 50 patients with duodenal ulcers who were on an ordinary diet. Forty others were placed on a bland diet. Truelove

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found no significant difference radiologically in the rate of healing of the ulcers or in the clinical responses of the ulcers in a 6 month follow-up period.

Buchman and associates[2] have recently reported the results of a controlled study of 113 patients. All patients admitted to his hospital with duodenal ulcer demonstrated on x-ray examination were included in the study. Alternate patients were given either a regular hospital diet or a bland diet. All patients were treated in the hospital. No anticholinergics were given. During the first week of therapy all patients, regardless of diet, received 30 ml. of antacid alternating with 30 ml. of milk each hour on the half hour during the day, and as required at night. During the second week of therapy the milk and antacid were alternated at hourly intervals and during the third week at 2-hourly intervals. Buchman et al. found that ulcer healing, disappearance of symptoms, and recurrences at one year were no different between the two groups of patients. They did not use randomization in their selection of patients, and felt that this defect was eliminated by including every patient admitted to the hospital. They were aware of the defects of serial radiographs in determining complete healing.

Their study has been criticized because they used milk (a potent secretogogue for gastric acid)[35] and frequent and large amounts of antacid, which in the eyes of the reviewer was felt to have overwhelmed the effects of deleterious diet in the treatment of the ulcer. Further, it was noted that their patient population (Veterans Administration Hospital) might have introduced other variables, such as alcoholism, not commonly found in the general population.[10, 37]

Roth and Caron[32] evaluated the concepts of patients as to what should constitute an ulcer diet and what such diets were expected to accomplish. Their study revealed that patients had little knowledge as to the basis for an ulcer diet. They were not aware of the concept of acid control, and tended to attribute the effectiveness of the diet to avoidance of foods which they thought might irritate the stomach.

Donaldson and Koch[19] evaluated 655 patients with gastrointestinal diseases. They compared reports of symptoms obtained from the patients by an independent investigator with diagnoses as determined by a chart review. They questioned patients specifically about food intolerances. They found that there was no characteristic pattern of food intolerance in patients with duodenal ulcer. They also found that dyspeptic symptoms were much more common in patients with peptic ulcer than in patients with biliary tract disease.

Ulcer diets have been composed of foods supposedly unable to elicit large acid outputs. Code and others[35] have studied total output of acid from vagally innervated pouches of dogs fed common foods. They discovered that foods with the greatest content of protein (milk one of them) stimulated the greatest output of acid. In subsequent studies, Kotrba and Code[20] demonstrated that except for egg albumen the quantity of acid secreted is directly related to the buffering capacity of the food administered.

Weinstein and co-workers,[11] in an evaluation of diet in relation to gastrointestinal function, reviewed 18 diet manuals. They found wide

discrepancies between the diets prescribed in one manual and similar diets in another.

While there seems to be much controversy about the significance of diet in patients with peptic ulcer, investigations have revealed that there is a scientific basis for avoiding certain foods. Among these foods, beverages containing alcohol and caffeine (coffee, tea, and cocoa) are the most important. Roth and Ivy[33] studied the effects of caffeine sodium benzoate administered by nasogastric tube to volunteers. They discovered that in those subjects with peptic ulcer there was a marked and prolonged increase in acid output. Further, in two healthy volunteers who put out high quantities of acid, ulcers developed in later years.

Harris and others[12] have demonstrated in an isolated frog mucosal preparation that methyl xanthine will stimulate the production of hydrochloric acid. This effect is due to the inhibition of the enzyme phosphodiesterase by xanthine. Phosphodiesterase is the enzyme which destroys cyclic adenosine monophosphate. They have discovered in their mucosal preparations that following the administration of caffeine there will be an increase in the content of cyclic adenosine monophosphate and that the increase of cyclic adenosine monophosphate in the mucosa parallels the amount of xanthine administered.

Alcohol has long been known to be an excellent gastric secretogogue. It is also a known gastric irritant. It was at one time used as a secretogogue in the study of gastric secretory capacity. Davenport,[7] in a series of studies beginning in 1956, used innervated oxynic pouches of dogs to demonstrate that salicylic acid in a non-ionizable form will allow a rapid flux of hydrogen ion through the mucosa of the stomach, while a simultaneous rapid flux of sodium will occur into the lumen of the stomach. The subsequent administration of alcohol will potentiate these changes.

DISEASES TREATED WITH LOW RESIDUE DIETS

High and low residue diets are prescribed because of their supposed ability to alter the stool. Kramer[21] examined this concept in an editorial in 1964. He found that there were marked differences in opinion among various physicians in his hospital about what constituted a low residue diet. In a subsequent examination of several well-known diet manuals, he found the same widespread difference between one manual and the next.

A major problem has been the definition of the term residue. It was originally defined as that fraction of food not enzymatically digested by the intestine. The indigestible fraction was found to be composed predominantly of cellulose, hemicellulose, and lignon. This fraction has also been described as roughage or bulk.

Foods high in crude fiber content have been found to affect the intestine in several ways. First, the bulk of the food in itself mechanically stimulates intestinal motility. This can be detrimental in patients with strictures of the bowel or other obstructions. Foods high in crude fiber content (particularly hemicellulose and to a lesser extent cellulose) are, in addition, broken down by intestinal bacteria to volatile fatty acids,

which act as potent irritant cathartics. Finally, crude fiber can imbibe water, i.e., it can act as a hygroscopic agent. An example of this type of reaction is seen in agar.

Kramer noted that because of the widely differing mechanisms of action of bulk in the intestine, the term residue is actually used to describe two separate phenomena – one which depends upon the indigestible fiber of foods, and one which leads to increased fecal output by mechanisms other than the mechanical action of indigestible fiber (prunes, an example of this latter type of food, produce an increase in fluid output because they contain a laxative principle, diphenyllisatin).

Rubner[31] has studied the effects of placing subjects on single items of food and measuring their subsequent fecal output. Unfortunately, these experiments led to anorexia and actual nausea in some subjects. The experiments were poorly tolerated by many because of the monotonous nature of the diet and the types of foods which had to be ingested. Hosoi and others[16] used a preparation for dogs, with an ileorectal anastomosis. He fed the dogs different types of foods and studied their fecal output. This type of experiment again can be faulted because dogs are carnivorous, and humans are omnivorous, and also because dogs are creatures of habit, tending to eat the same diet from day to day.

In an attempt to circumvent these problems, Kramer et al.[22] studied the effect of bulk in diet on healthy ileostomized subjects who were first fed a diet carefully selected to avoid such bulk factors. To this diet they added the various foods to be studied, after first establishing what each patient would produce in stool bulk on the baseline diet. Kramer noted that the ileostomy introduced another variable into the experiment – the absence of normal colonic bacteria. As noted, this removes one of the important actions of bulk on the intestine, i.e., that of the laxative effect of volatile acids produced by the bacteria of the colon on the bulk. Kramer found that foods high in crude fiber were laxatives, but he was not able to confirm previous studies which had indicated that selected foods of low fiber content increased fecal output (with the exception of prune juice which, as noted above, contains a specific laxative element).

Diverticular Disease of Colon

Recently, new light has been shed on diverticular disease of the colon. Carlson and Hoelzel[3] studied litter mate rats fed high and low residue diets. They found that the rats fed the low residue diets developed diverticula, while those fed a normal rat high residue diet did not. Wells[32] has reported a low incidence of diverticular disease in West African natives who normally eat a high residue diet. The same findings have been noted in Korea by Kim,[18] who reviewed 500 radiographs of the lower bowel and in only one instance found a diverticulum.

Painter and Truelove[29] have performed some interesting studies of colonic pressure changes in patients with colonic diverticular disease. Utilizing the combination of intrasigmoid manometry (open tip tubes) with cineradiography, they demonstrated that these patients will develop pockets of high pressure in the colon secondary to segmental contractions of the bowel. They suggested that such segmental contractions occur more commonly in patients on a low residue diet because of the

ability of the colon, in the absence of residue within its lumen, to completely contract, producing isolated segments of high pressure.

Morson[17] has described thickening of the tinea coli of segments of bowel containing diverticulae, as well as thickening and a corrugated appearance of the circular muscle of such bowel. He found evidence of concomitant inflammatory changes in only 66 per cent of 103 specimens examined. On the basis of this data, Almy[1] has suggested that perhaps diverticular disease should be treated with a high residue diet plus large amounts of hydroscopic colloids to prevent apposition of the colonic wall and development of segments of high pressure.

Ulcerative Colitis and Regional Enteritis

Idiopathic ulcerative colitis has been treated with a low residue diet. There is currently no evidence to suggest that such a diet has any beneficial effect. Recent work, however, has suggested that avoidance of milk may have a definitive effect in some patients with ulcerative colitis. Truelove and Wright[44] have evaluated three therapeutic diets in patients with ulcerative colitis. These diets were a milk-free diet, a gluten-free milk-free diet, and a dummy diet. In the milk-exclusion groups, fewer patients were removed from the study because of relapses. Twice as many patients on the milk-free diet went a year without relapses when compared to the control group on the dummy diet. Particularly impressive was the fact that results from the group studied during their initial attack suggested that about one in five patients can be expected to respond to removal of milk from their diets. Of ten patients who maintained complete remission on a milk-free diet, four suffered relapses when challenged with milk. On the basis of a positive correlation between whole milk and titers of lactalbumen antibodies in the serum and the relapse rates of patients with ulcerative colitis, Truelove and Wright postulated a possible immunologic basis for the affects of milk. They did note that the correlation might have been associated simply with the increased mucosal permeability produced by the disease process. They were able in another study to show a close but not perfect correlation of sigmoidoscopic changes and rectal biopsies with the avoidance or the administration of milk.[45]

Another possible basis for the effect of milk in ulcerative colitis has been the suggested depletion of intestinal lactase secondary to the involvement of the bowel by the ulcerative colitic process. Truelove and others[36] have shown on small bowel biopsy that microscopic changes do occur in patients with known involvement of the large bowel by ulcerative colitis. Newcomer and McGill[28] determined intestinal sucrase, lactase, and maltase levels in 24 patients with ulcerative colitis from specimens obtained from region of the ligament of Treitz. They found that two of the 24 patients had an isolated lactase deficiency, an incidence of 8.3 per cent. In a previous study in 100 normal Caucasians they had found an incidence of 6 per cent spontaneous lactase deficiencies. They did not feel that this was a significant difference but did recommend that patients with a history of milk intolerance who had ulcerative colitis should have milk removed from the diet while they were acutely ill.

Chalfin and Holt[4] found abnormal oral lactose tolerance tests in four of nine patients with regional enteritis and in four of eleven with ulcerative colitis. At least five of these patients gave a history of prior milk intolerance. Two of twelve normal subjects studied at the same time showed abnormal lactose tolerance tests. Small bowel enzyme assays were not performed.

Struthers and others[38] reported two patients with milk intolerance. One had regional enteritis and the other ulcerative colitis. Both had abnormal lactose absorption as measured by a lactose tolerance test. A small bowel lactase assay was done only in the patient with ulcerative colitis but this was abnormal. Abnormal amounts of lactic acid were found in the stools of both.

DYSPEPTIC SYMPTOMS AND CHOLECYSTITIS

Although intestinal symptoms are often attributed to gas, the volume, composition, and rate of accumulation of such has never been quantitated. Levitt and Inglefinger[23] have recently developed a method for such studies and have shown that the old saw that baked beans are producers of gas has scientific validity. Their method of evaluation consisted of a washout technique. They infused argon at a known rate and quantitatively collected the expired rectal gas. Swallowed air was removed by an indwelling nasogastric tube. The gas so collected was then analyzed for nitrogen, hydrogen, oxygen, methane, carbon dioxide, and argon. They showed that the volume of gas normally present in the human bowel as determined by the dilution of their argon marker was quite small, and that the bowel contents were generally anaerobic. Gastrointestinal bacteria utilize oxygen and produce carbon dioxide, methane, and hydrogen. Most interestingly, it was demonstrated that after the ingestion of baked beans a large amount of gas was produced by the intestinal bacteria. Richards and others[31] have also studied the mechanisms of gas formation utilizing a dog preparation of intestine. They injected a bean substrate into isolated loops of the intestine. They found that both in the isolated bowel and when intestinal bacteria removed from the loops were incubated in vitro with bean substrate, large amounts of carbon dioxide and hydrogen were produced. Further antibiotics would inhibit such gas production.

Symptoms of bloating, belching, and dyspepsia have been held to be due to cholecystitis. As a result, a diet low in fried and greasy foods has been advocated. Hinkle and Moller[13] interviewed 1000 patients referred for cholecystography and found that these symptoms were no more common in those patients with abnormal results than in those with normal cholecystograms.

Price[30] evaluated the alleged relationship between gallbladder disease and dyspeptic symptoms by interviewing 146 women, ages 50 to 70, about the presence or absence of such symptoms. He subsequently obtained x-rays of the gallbladder in these women. He found dyspeptic symptoms in 53 per cent of those with normal and in 50 per cent of those

with abnormal cholecystograms. The various dyspeptic symptoms and their degree were, moreover, evenly distributed amongst the normal and abnormal gallbladder groups. The incidence of intolerance to fried and fatty foods was even more noteworthy in that 28 per cent of the group with normal gallbladders, compared to 4 per cent of those with abnormal results, complained of this symptom.

Taggert and Billington[39] studied 12 subjects who complained of digestive symptoms attributed to foods fried or baked in fat. The subjects were fed meals in which the fat was so disguised as to not be recognizable. Ninety-two per cent of the subjects were unable to recognize by symptoms the presence of the type of food of which they had complained. It was concluded that the symptoms were not related to the fat ingested but rather to prejudices about fat.

LIVER DISEASES

Diet has been felt to be an important aspect of the treatment of liver disease. Chalmers and others[5] studied the effect of diet in hospitalized military personnel with acute hepatitis. They found that patients who were forced to eat a diet high in calories (3000 per day) and protein (150 gm. per day) and supplemented with choline and multiple vitamins did better than comparable personnel who were allowed to eat a regular hospital diet. In a subsequent study they observed that the duration of hepatitis was shorter for those forced to eat a high protein diet (19 per cent protein calories) than those on a normal protein diet (11 per cent protein calories). The duration of illness was similar in those eating 3000 calories and those eating 4000 calories per day, and also in those receiving and not receiving supplementary choline and vitamins. Asymptomatic laboratory relapses occurred with equal frequency in both groups. There was a more rapid decline of serum bilirubin in the high protein groups of both studies.

Crews and Faloon[6] evaluated the evidence for and against the restriction of fat in liver disease. They concluded after an extensive search of the literature that there was no evidence to support the concept that fat was harmful. Further, they noted that a certain amount of fat was necessary to make a diet palatable. Fat is a ready source of calories. Certain fatty acids may be essential. The addition of fat to the diet aids in the absorption of fat-soluble vitamins. They noted that there was no evidence that low fat diets were helpful in liver disease, and that most of the data to support such a concept had been based on the presence or absence of symptoms such as anorexia, often an accompaniment of liver disease itself regardless of the diet prescribed.

Hoaglund[11] evaluated the effects of varying the amount of fat intake on the return of the bromsulphalein to normal following hepatitis and found that a liberal fat diet (150 gm. per day) led to a more rapid return than a low fat diet. Similar studies by Wilson et al.[13] and by Mindrum and Schiff[26] have confirmed this finding.

CONCLUSIONS

An attempt has been made to review what is and is not known about the current place of diet in some of the more common gastrointestinal diseases. The data reviewed suggest that in many such disorders diet therapy has been based in the past more on traditional lore than on sound scientific principles.

Problems exist in experimentally assaying the effects of diet on symptoms. Claims by patients that specific foods cause specific complaints are difficult to assess because their interpretations are often colored by personal bias, tradition, and emotional background. In those diseases in which a scientific basis for treatment exists, such as gluten enteropathy, patients are unable to identify what foods are harmful unless they are given specific instructions.

Recent work has emphasized the need for carefully controlled scientific investigation. Certainly, data being studied today do not indicate a need for therapeutic nihilism in regard to all diets, but rather for some degree of skepticism in regard to those dietary measures which have been proved only by tradition.

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Surgical Nutrition

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"Surgical nutrition" is a convenient but inaccurate description of a part of patient care concerned with maintaining normal body composition in the face of reduced intake, increased metabolic demands, or disordered metabolic machinery. In actuality, it is neither entirely surgical (septic starvation occurs on medical and pediatric as well as surgical hospital wards), nor is it a field of nutrition in the strict sense. It is a factor in the treatment of only a fraction of hospital patients, for most individuals with normal nutritional reserve who undergo treatment of an acute illness can tolerate a period of reduced caloric and protein intake perfectly well, and no special measures are required. But, for an occasional patient, careful nutritional handling is necessary for survival. The situation is in some ways analogous to obstetrical practice, where the usually normal processes of childbirth are ordinarily only monitored and assisted, although when intervention does become necessary, the need for it may be urgent. To know when to intervene nutritionally, we need some basic information, namely, body stores of available fuel, an appreciation of the events that occur in the course of starvation in otherwise normal man, and some knowledge of the ways in which the sick differ from the normal in their response to reduced food intake.

THE METABOLIC RESPONSE TO STARVATION

Body Composition: A Measure of the Fuel Supply

Patients begin an episode of illness with a stock of macronutrients that can be measured or simply estimated with reasonable accuracy, and

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which will be expended (during the illness) according to need. Endogenous energy resources are mostly comprised of stored carbohydrate, fat, and protein; of these, carbohydrate—which must be maintained in isotonic solution—is the least important. Over a long period of time, the few hundred to a thousand calories available from glucose and glycogen are negligible. Fat, which is anhydrous and hence energy-rich on a weight basis, forms the largest fraction of the caloric reserve, and the free fatty acids derived from its hydrolysis are adequate substrate for all but those few organs which have an absolute or a partial requirement for glucose. The protein stores are large, too, but not totally available; all body protein is consumed at some cost, since all is functional in some way.

Body compositional methods allow these components to be measured. Most schemes for determining the weight of body fat depend on its anhydrous property. For example, comparison of total body water with body weight, assuming a standard coefficient for hydration of the lean tissues, allows the weight of body fat to be calculated. A series of determinations in normal subjects has established a basis for its prediction, based on body weight, age, and sex as shown in Figure 1. Even though fat is the most variable component of body composition, guesses based on these data can be quite accurate. Some guidelines are that even in gross obesity, fat seldom exceeds half the total weight, while in healthy adult males, it is about a fifth of it. Women are fatter, fat averaging about 30 per cent of their total body weight. In extreme nutritional depletion, or at the point of death from starvation, the body may contain only 5 to 10 per cent fat.

Body protein is a different story. As a component of body composition, protein is more critical to survival in starvation than is fat. A starving organism can tolerate the acute loss of only a fraction of its visceral and muscle mass. For man, this fraction is not known with precision, but observation of animals suggests that something between a quarter and a third of body nitrogen will have been lost when death occurs; the data of Montemurro, et al. demonstrate this for rats (Fig. 2). These animal data could be obtained by carcass analysis, but determination of the total body protein in man is necessarily done indirectly. It is most practically measured in terms of total potassium. The total exchangeable potassium —which is very nearly the same as total body potassium—is measured and multiplied by appropriate factors that relate potassium to the nitrogen content of lean tissue, and in turn to body cell mass. Again, regression equations for its prediction are available from study of normal subjects as given in Table 1. They serve as a first approximation in estimating protein reserve.

Total caloric stores in individuals are very widely variable, and depend on another highly variable quantity: total body fat. Caloric reserve is impressively large when body composition is normal, and in obesity it is enormous, but in depleted states, energy stores may be small enough to be completely exhausted during the course of a short illness. Figure 3 shows examples from each extreme of this range: two women whose body weights are in the ratio of six to one, but for whom the ratio of caloric resources is greater than one hundred to one. The second pa-

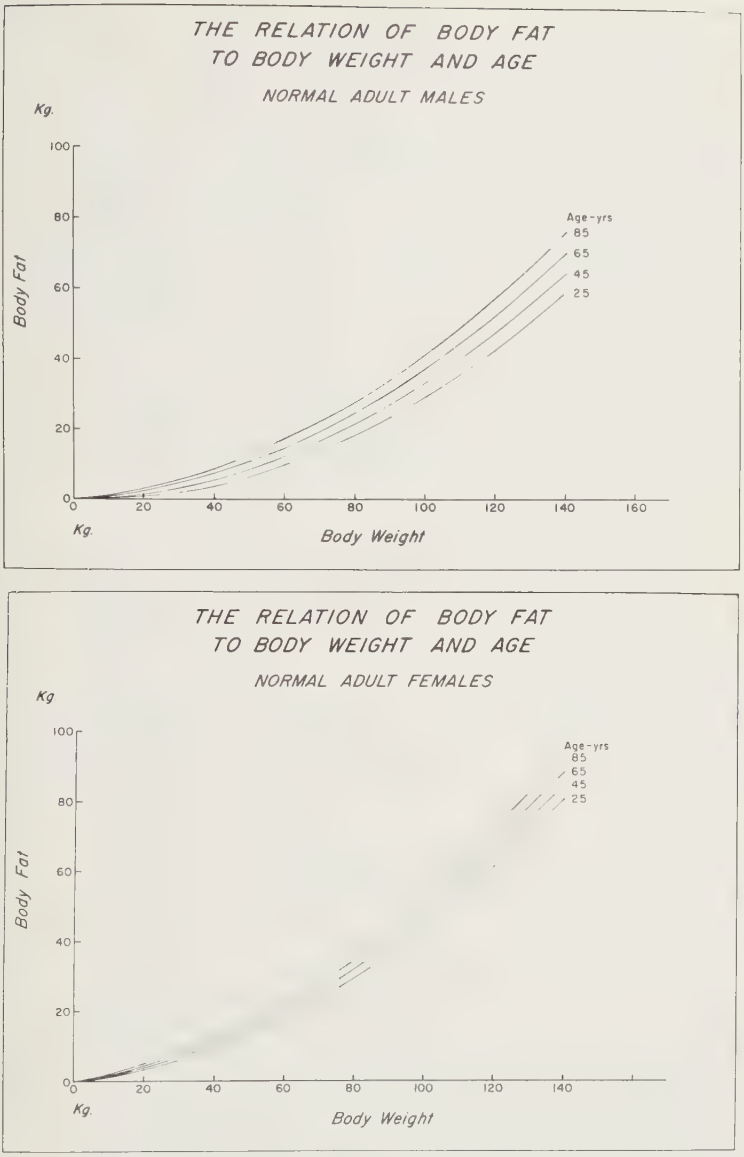

Figure 1. Body fat vs. body weight in normal individuals: a basis for guessing caloric reserve. Unsurprisingly, women are fatter than men, and fatness increases with age. *From* Moore et al., The Body Cell Mass and Its Supporting Environment. Philadelphia, W. B. Saunders Company, 1963.

Table 1. *Equations for Prediction of Exchangeable Potassium (K_e) from Body Weight (BWT)*

	AGE	EQUATION	95% CONFIDENCE LIMITS
Males	16–30	$K_e = 735 + 38.01$ (BWT)	± 23%
	31–60	$K_e = 1383 + 26.23$ (BWT)	± 20%
	61–90	$K_e = 723 + 27.20$ (BWT)	± 16%
Females	16–30	$K_e = 1250 + 18.30$ (BWT)	± 20%
	31–60	$K_e = 1176 + 16.93$ (BWT)	± 23%
	61–90	$K_e = 757 + 18.09$ (BWT)	± 29%

Body cell mass, in kilograms, equals milliequivalents of exchangeable potassium times 8.33.*

*Abridged from Moore, F. D., et al.: The Body Cell Mass and Its Supporting Environment. Philadelphia, W. B. Saunders Company, 1963.

tient, with a tiny nutritional reserve, is the sort of individual needing special nutritional management, particularly when that small reserve is coupled with increased demand. Although measurement of individual body composition may not be practical or appropriate for every patient,

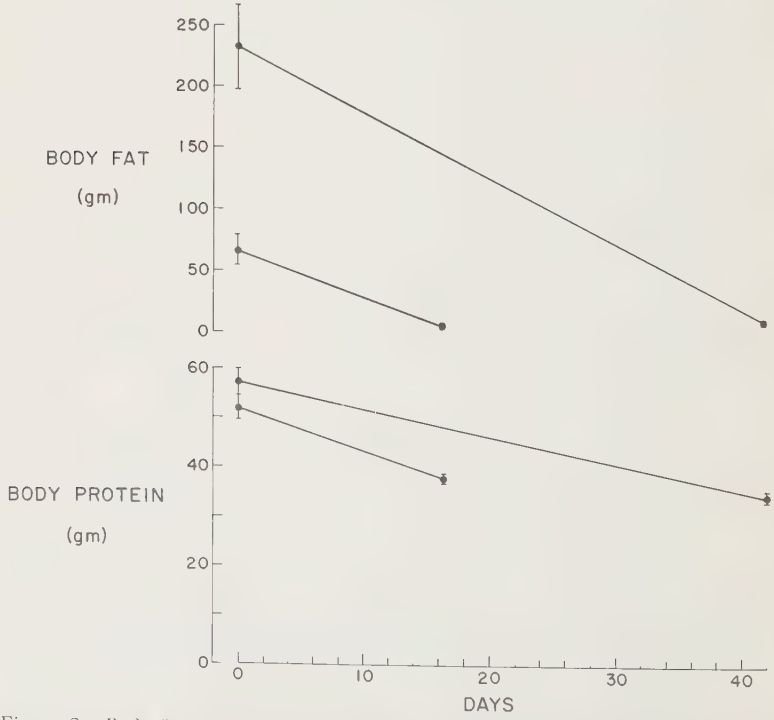

Figure 2. Body fat and protein by carcass analysis of normal rats and rats with hypothalamic obesity. Obese rats survive longer and at death are slightly but significantly fatter than the normal group. Both lose the same fraction of body protein. Data from Montemurro.

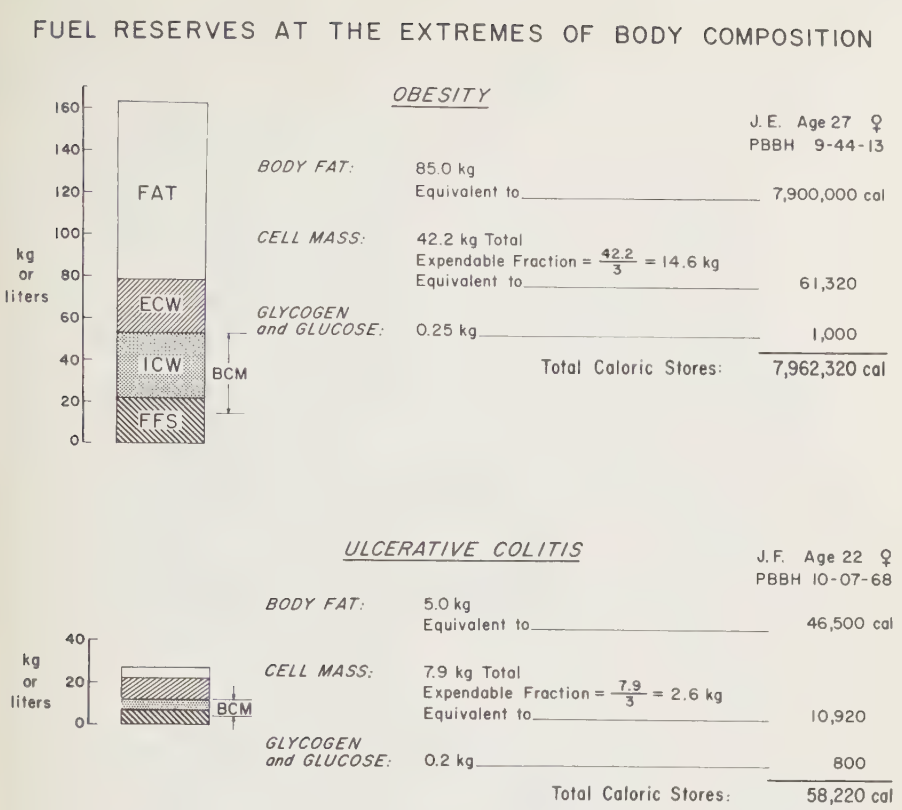

Figure 3. Body composition in very fat and very thin individuals. Fat derived from total body water measurement by tritium dilution; extracellular water (ECW) from bromide space; intracellular water (ICW) = total water minus ECW; body cell mass (BCM) from exchangeable potassium; fat-free solids (FFS) = body weight − (fat + water).

studies in selected patients are useful to fix the borders of the clinical range of individual variation, and to establish indications for treatment.

Energy Expenditure and Nitrogen Loss: The Rate of Fuel Consumption

When a patient has been deprived of normal food intake, the rate at which stored fuel is burned depends on the total requirement for calories, the need for special substrate (i.e., glucose), and the success of adaptive mechanisms that attempt to limit consumption of endogenous protein. These latter are normally very effective. The series of events that take place when food intake stops has been delineated by Cahill and associates[3] and are summarized for one individual in Figure 4.

This patient weighed 154 kg., but he was not just obese; body compositional measurement showed him to be, underneath his fat, a large

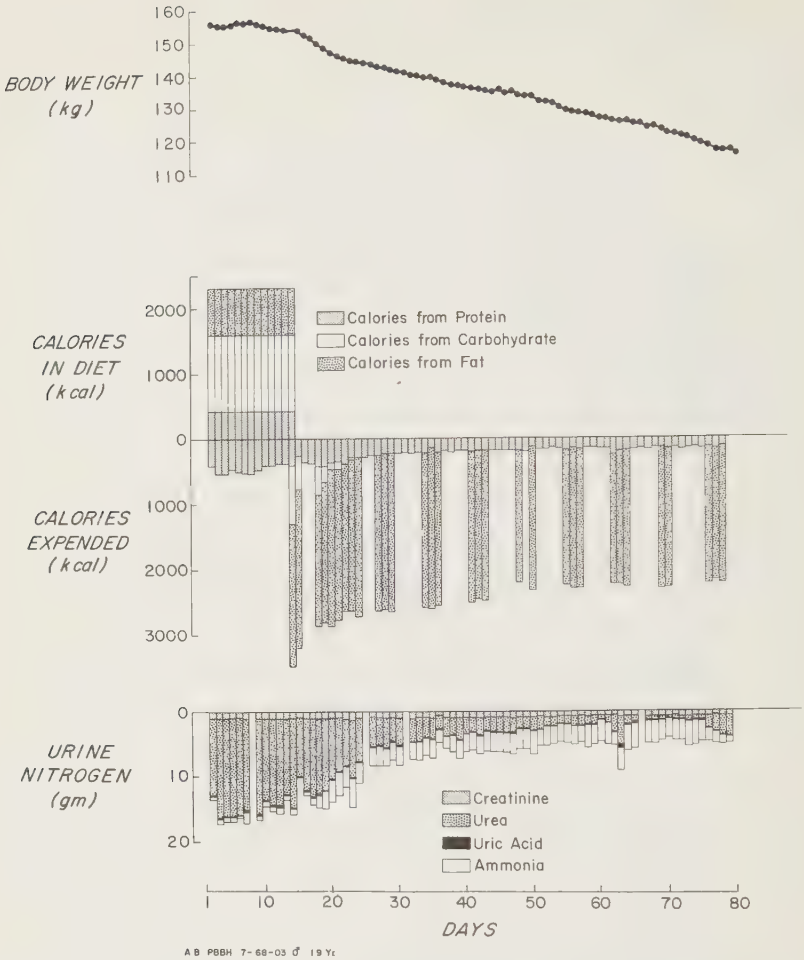

Figure 4. Changes in weight, energy balance, and urine nitrogen during a 65 day fast. Expended calories were measured by indirect calorimetry, a 5 minute expired air sample being collected each hour during the waking day.

muscular man. His body cell mass measured 49 kg., or 32 per cent of his body weight. In the fed state, his urine nitrogen excretion averaged 18 gm. per 24 hr., an equilibrium value determined principally by composition of the diet. With the beginning of fasting, urine nitrogen fell, at first rapidly, then more slowly, to about 4 gm. per day. This value reflects utilization of 120 gm. of the body cell mass; so small a figure is attainable only by adaptation of the central nervous system toward utilization of ketones as part of the brain's substrate requirement, thus sparing glucose, which in the fasting state can be obtained only from amino acids. This subject's total fuel requirement of course continues during his fast, although it is reduced somewhat over prefast levels, and protein oxida-

tion or protein-glucose interconversion with subsequent terminal oxidation contributes little to the total caloric expenditure. Most of the energy requirement is provided by fat oxidation, evidenced by a non-protein respiratory quotient of 0.70, plasma-free fatty acid levels in excess of 2000 microEq. per liter, and the simple fact that there is nothing else to burn.

With this rate of fuel consumption, based on an estimation of his body fuel reserves, it can be predicted that this individual would survive a total fast of 6 months' duration.

On the other hand, the second patient of Figure 3 would not tolerate fasting very much more than a week. Her nitrogen losses during one septic episode measured 10 gm. per day; if the expendable fraction of body cell mass is taken to be 2.6 kg., she could lose only 86 gm. of nitrogen before reaching the degree of nitrogen depletion associated with death from starvation.

These calculations are hard to confirm. The possible duration of simple starvation beginning with normal body composition is not really very well known. In spite of the multitudes who have died of malnutrition, complete starvation is not very common. Some confirmation of the proposition that fasting obese patients are not a special case is gained from reconstruction of prolonged voluntary fasts. One of the longest recorded for a normal man was endured by Terence MacSweeney, an Irish patriot who began a hunger strike after his arrest in August, 1920. He died 72 days later, without having been forcibly fed; this is exactly the survival time that would be predicted from rough estimates of body composition based on his weight and age.

In the hospitalized patient, several effects operate to modify this bookkeeping kind of approach, although it is useful in gaining an approximate idea of the general magnitude of fuel stores and fuel expenditure. One is the administration of small amounts of glucose in conventional isotonic intravenous fluids. Although calorically inconsequential, its nitrogen-sparing effect is important. On the other hand, the rate of substrate expenditure may be substantially increased over that observed in the absence of disease. Finally, it is of course recognized that the medical objective is not simply to prevent death from starvation, although that eventually undoubtedly does occur in some hospitalized patients, but to prevent the effects of nutritional depletion on organ function and reparative processes. The point at which these less tangible effects become important is difficult to identify; it is certain only that it is some point short of total starvation.

VARIATIONS FROM NORMAL IN DISEASE AND AFTER INJURY

Although it has long been recognized that sick patients respond to starvation abnormally, and that the abnormal response results from a combination of factors rather than a single mechanism, here too the

body's handling of nitrogen is a critical process. Some components of the altered response are changed energy requirement, abnormal extrarenal nitrogen losses, and failure of endocrine mechanisms normally effective in nitrogen conservation. All are discussed briefly in subsequent paragraphs, but one additional factor is so obvious as to be sometimes overlooked. It is that sick people do not feel well. Weakness, pain, depression of appetite, and sedation by drugs—all challenge the dietician's skills. Patients with large thermal burns are one of the best examples; often they can be fed adequately through their whole course. What can be done when standard nutritional methods are energetically pursued was well documented by the work of Sutherland et al.,[12] in which a group of 30 burned children were maintained in generally positive nitrogen balance with only brief periods of negative balance, in spite of the hypermetabolism, extrarenal nitrogen loss, and septic catabolic effects associated with burn trauma. This was accomplished almost entirely with feedings by the oral route, and by tailoring the form of the diet to the patient's needs, which in many cases required an all-liquid diet rather than solid food.

Increased Energy Expenditure

Energy expenditure, and hence caloric requirement, is decreased during fasting (Fig. 4). It changes very little after routine, uncomplicated surgical procedures, but may increase substantially in response to sepsis and trauma of greater magnitude than that associated with a well-conducted operation. Oxygen consumption is increased by fever alone, but not by very much—about 7 per cent per °F. If increased out of proportion to the expected fever-induced response, it reflects the greater work requirement imposed on the patient by any of several demands for energy: thermal (endocrine stimulated hypermetabolism or increased heat loss), respiratory, or cardiac work. Sometimes, abnormal energy requirements can be reduced. The burned patient's evaporative heat loss is decreased by maintaining high ambient humidity and supplying radiant energy. The work of breathing is reduced by mechanical ventilation. Efforts to control seizures, shivering, and hypermetabolic delirium tremens are part of ordinary treatment.

In these situations caloric requirement can be considerably greater than the resting energy expenditure, perhaps doubled,[10] and calories in excess of the basal requirement must be supplied if nutritional balance is to be achieved. Forty calories per kilogram per 24 hours is usually adequate; more calories are needed for infants or in the exceptional situations above.

Extrarenal Nitrogen Loss

Normally, 95 per cent of the nitrogen lost from the body is in the urine; 80 per cent is urea, and a variable fraction is present as ammonia, depending on the acid-base status, with the small remainder in miscellaneous constituents: creatinine, uric acid, and so on. A small percentage of ingested nitrogen can be recovered in feces, and a tiny quantity is lost by skin exfoliation and similar routes. In disease, other losses may be

increased, and can equal nitrogen excretion by the renal route; because extrarenal nitrogen is usually lost as unmetabolized protein, there is no compensatory reduction in nitrogen catabolism. Exudative burns, protein-losing enteropathy, and malabsorption states are all examples. In short bowel syndromes, however, nitrogen loss is usually not the problem that caloric, fluid, and electrolyte balance may be. Nitrogen absorption is efficient in relatively short lengths of otherwise normal small intestine.

METHODS OF TREATMENT

A decision to undertake special nutritional support is based on comparison of nutritional reserve with the rate at which that reserve is depleted; after the decision is made, several options for treatment are available. The choice depends in large part on the functional status of the gastrointestinal tract; it is not always necessary to undertake total parenteral nutrition, and often the patient's nutritional needs will be met by simple standard routines: careful choice of appetizing, mechanically suitable food, or addition of dietary supplements. Beyond this, there are three types of special food that offer particular advantages to surgical patients: medium-chain triglycerides, nutritionally complete soluble diets, and total parenteral nutrition.

Medium Chain Triglycerides

Medium chain triglycerides were introduced to clinical nutrition by Hashim[7] 10 years ago, and their properties have since been exploited in a number of acute surgical malabsorptive states, as well as more chronic nutritional problems. Medium chain triglyceride (C6-10) is not only easily hydrolyzed (in fact one of the problems of cooking with the material is its ready hydrolysis when heated) but can be absorbed with no intraluminal hydrolysis at all. After absorption it is partitioned almost entirely into the portal blood as free fatty acids rather than chylomicrons. Absorption is possible with shorter lengths of small bowel or more rapid transit time than for ordinary food triglyceride. The basic use for this material is to provide calories (at a rate of 8.4 calories per gram) to compensate for impaired fat absorption. There can be secondary advantages in reduction of stool bulk and the foul quality of stools in steatorrhea.

The dose is adjusted to tolerance and requirement; in surgical patients it is usually given as an oily liquid or tube fed; for long-term use, where palatability can be a considerable problem, flavored or powdered preparations are available. Their principal disadvantage is their lactose content, which may not be tolerated by patients with short small bowel.

As implied above, a major surgical application is in treatment of short bowel syndromes and internal or external fistulas. Results in short bowel syndromes are variable: diarrhea can sometimes be increased. The patient J. F. of Figure 3 is an example of a good result. This young lady, with very fulminant ulcerative colitis and ileitis, survived a total colectomy and then a series of small bowel resections, intraperitoneal abscesses, and fistulas with about two thirds of her small bowel intact

and, of course, no colon at all. Ileostomy volumes were high, transit time was rapid, and on a constant diet containing slightly less than 70 gm. of ordinary triglyceride, only 27 per cent of ingested fat was retained, as shown in Table 2. The addition of medium-chain triglycerides increased fat absorption to a level consistent with adequate nutrition. It should be noted that ordinary methods of fecal fat measurement are not satisfactory for determination of medium-chain triglycerides in stool; unless appropriate extraction methods are used, not all of the excreted triglycerides will be recovered.

Elemental Diets

Solutions of L-amino acids and sugar with appropriate minerals and micronutrients form a distinct category of nutritional material, a category made practical by the commercial availability of amino acids in nutritional quantity at reasonably low cost. This material is quite unlike conventional liquid diets and tube feeding mixtures which contain substantial quantities of fat, protein, and peptides—substances which require hydrolysis for absorption. (One elemental diet does contain a small quantity of linoleate, a possible nutritional requirement.)

Elemental diets have substantial advantages. They are chemically defined and consequently allow the quantitative observation of metabolic balance to approach being a practical part of routine patient care. Since they are essentially fat-free, pancreatic stimulation could be expected to be minimized, and data being developed by Stevens and Randall[11] confirm this. The zero residue property and diminished enteric secretion together can result in reduced output from fistulas (when they exist), and usually in sharply decreased stool volume. One hazard associated with gastric instillation of other types of tube feeding mixtures which contain large amounts of fat is delayed emptying and the possibility of aspiration; this risk is reduced with the soluble diet.

There are some disadvantages. These materials are usually very hypertonic, the precise tonicity varying with the form of the carbo-

Table 2. *Absorption of Medium Chain and Normal Dietary Triglyceride after Ileal Resection*

DAY	JEJUNOSTOMY VOLUME (ML.)	DIETARY FAT (GM.)	MCT (GM.)	TOTAL FAT ABSORPTION
1	4030	68.2	0	28.8%
2	3825	69.5	0	26.7%
3	3400	68.2	0	33.1%
4	2970	69.5	0	27.4%
5	3800	68.2	0	20.8%
			Mean:	27.4%
6	4200	69.5	180	32.0%
7	5375	68.2	180	56.9%
8	4650	69.5	180	58.3%
9	5150	68.2	180	58.1%
10	3400	69.5	180	62.2%
			Mean:	53.5%

hydrate furnished and the dilution, but it may exceed one osmole per liter. Patients need gradual introduction to this osmolar burden to avoid symptoms similar to those seen in the dumping syndrome: osmotic diuresis, diarrhea, and those consequences of solute loading that occur if normal thirst mechanisms are impaired or adequate free water intake is not available. Further, more than 90 per cent of the caloric value is derived from carbohydrate; the nitrogen content (about 3 gm. for an average 24-hour intake) is insufficient to replace large losses. And the taste of current products, though far preferable to the unflavored state, is not tolerated by some individuals. Generally speaking, large quantities given for long periods are best administered by feeding tube.

The role of elemental diets lies somewhere between that of total parenteral nutrition and that of normal food. Its potential in the treatment of chronic pancreatic disease and of ulcerative colitis is intriguing. The hazards of prolonged venous intubation are avoided, but some gastrointestinal function is necessary.

Total Parenteral Nutrition

The ability to completely bypass gastrointestinal absorption in supplying adequate nutrition is a significant medical advance. Two years ago, Dudrick, Wilmore, Vars, and Rhoads[2] first demonstrated that the intravenous infusion of a fat-free amino acid glucose solution could support normal growth and development. Their method, with or without slight modification, has now had wide clinical use and has been shown to be effective in both adults and small infants.[2, 4]

The method depends on the infusion of glucose for calories and a protein hydrolysate as a source of nitrogen. This mixture is prepared in the hospital pharmacy by mixing commercially available preparations of 50 per cent glucose and 5 per cent protein hydrolysate. The final solution contains 20 per cent glucose and 3.5 per cent protein equivalent (in the form of amino acids and polypeptides), and 0.94 calories per ml. Appropriate vitamins and minerals are added as described elsewhere.[2, 4] Electrolyte concentrations are tailored to the needs of the individual patient. To provide trace elements and essential fatty acids which are not present in the mixture, supplementary plasma or blood transfusions are given twice weekly.

The daily volume administered depends on the patient's age and clinical status. Generally, daily infusions containing 125 calories per kg. per day and .74 gm. of nitrogen per kg. per day for infants, and 35 to 50 calories per kg. per day and 0.2 gm. nitrogen per kg. per day for adults are sufficient. Some patients with intense catabolic drive will require even more nitrogen than this generous budget allows. Nevertheless, the total fluid load and the patient's ability to metabolize the very large glucose load define the maximum dose of infusate. This hypertonic infusate (approximately 2500 milliosmoles per liter) must be delivered through a central venous catheter to avoid peripheral venous inflammation and thrombosis. In the infant, cannulation of the superior vena cava is best performed by a cutdown at the internal or external jugular vein as shown in Figure 5. In the adult, percutaneous subclavian vein puncture

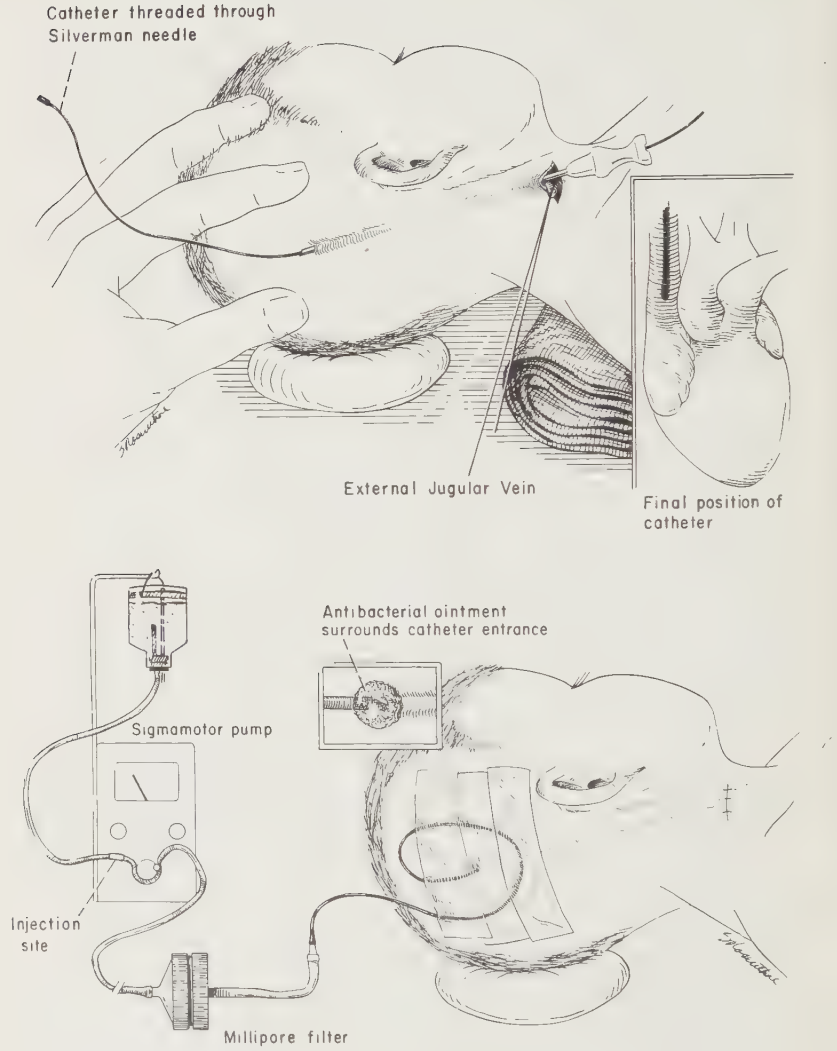

Figure 5. Technique for delivering hypertonic intravenous diet in an infant. *Above* Method of placing silicone rubber catheter in a subcutaneous tract before its insertion into the jugular vein for final placement in the superior vena cava. *Below*, Infusate, constant infusion pump, and bacterial filter attached to the properly secured central venous line.

and cannulation has generally been used. For long-term use, soft silicone rubber catheters cause far less inflammation than the usual intravenous catheters, and therefore are less likely to cause thrombosis or perforation of the vena cava. Proper position of the catheter tip is essential and can be confirmed radiographically by the use of a radiopaque catheter or one filled with contrast material. The infusate must be administered at a uniform rate over 24 hours to insure proper utilization of the very large quantities of glucose. This is most readily accomplished by the use of a variable rate constant infusion pump, especially when a bacterial filter which adds resistance to the circuit is employed.

To evaluate the patient's response to therapy, the clinical measurements which have been most helpful include daily weight, accurate volumes of urine and other body fluid losses, qualitative urine sugar concentrations, blood sugar levels and serum electrolyte content and osmolarity. In most patients, the large quantity of glucose is tolerated without the addition of insulin. Quantitative glucose and amino-acid excretion studies have shown less than 1 per cent of the glucose and amino-acids infused are lost in the urine.[1] However, in the child, even this minimal glycosuria can result in a 3+ urine if tested by the Clinitest method.

The most serious potential complication is sepsis. Candida albicans has been the most frequent offender.[5] Organisms may enter the blood stream via the catheter tract or from a contaminated intravenous solution. The catheter, a foreign body in the blood stream, may perpetuate the growth of bacteria which enter the blood stream at a distant septic site. Measures aimed at minimizing the risk of sepsis include: (1) aseptic preparation of the infusate; (2) use of an operating room for the placement of the central venous line when cannulation by a cutdown technique is necessary; (3) tunneling of the catheter subcutaneously for a distance of 2 to 4 inches between the skin entry site and the vein entry site; (4) use of a bacterial filter in-line to remove microorganisms which may have contaminated the solution; (5) meticulous care of the skin about the catheter entry site with sterile dressing changes, skin disinfection and the application of a bactericidal and fungicidal ointment every 3 days;[6] avoidance of blood sampling from or unnecessary uncoupling of the venous line;[7] removal of the catheter when sepsis is suspected.

Observations for the development of straightforward or subtle metabolic problems are always necessary. Although most patients are able to utilize this intravenous diet, an occasional patient will exhibit hyperglycemia, glycosuria, and an osmotic diuresis which often responds to the addition of insulin or temporarily decreasing the glucose load. Excessive aminoaciduria resulting in abnormal losses of water and solute may occur in the very small infant or in an older patient with abnormal renal function. Large quantities of potassium may be required particularly by the severely depleted patient when extracellular potassium moves into cells with improved nutrition. Despite what seems to be adequate nutrition, unrecognized and poorly defined nutritional deficiency states may occur especially in those fed intravenously for prolonged periods.

Figure 6. This 4½ month old infant had been treated and evaluated at several hospitals for chronic nonspecific diarrhea. Despite usually successful medical therapy, diarrhea persisted and he failed to grow. Intravenous alimentation was instituted to provide calories and nitrogen for growth and adequate repair of his intestinal lesion. His intestinal tract was put to rest for 30 days, and thereafter progressive oral feedings were started. Intravenous feeding was discontinued after 55 days, at which time gastrointestinal tract function was sufficient to maintain adequate nutrition. *Above*, The infant at the start of intravenous feeding. *Below*, After 55 days of intravenous feeding, there has been a weight gain of 1.5 kg. and a positive nitrogen balance of between 150 and 300 mg. per kg. per day.

It can be anticipated that total parenteral nutrition will soon become simpler. Ready mixed sterile solutions will be a great convenience. A new intravenous fat emulsion, used widely abroad, appears to be safe and without the undesirable effects seen with previously available fat emulsions. It offers the great advantage of allowing a calorically adequate mixture to be administered via peripheral vein.

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Diagnosis and Dietary Treatment of Blood Lipid Disorders

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Intensive investigation during the past decade has provided new insights into our understanding of the disorders of lipoprotein transport, and their possible relationship to the process of atherogenesis. It is now quite clear that the measurement of either plasma cholesterol or triglyceride levels alone is inadequate for proper clinical evaluation of hyperlipidemia. The major plasma lipids can no longer be approached simply in terms of the total circulating cholesterol and triglyceride concentrations, but should be considered as part of lipoproteins, the macromolecular complexes in which these lipid moieties circulate. Since hyperlipidemia may result from defective protein as well as lipid metabolism, recent efforts to systematize the varied disorders of lipid transport on the basis of specific and distinctive lipoprotein characteristics have provided a useful new diagnostic and therapeutic approach to patients with elevated plasma lipids.[5] In this review, mechanisms involved in the normal regulation of lipid transport in plasma in man will be reviewed briefly in order to provide a physiologic basis for subsequent consideration of some of the better defined disorders of lipoprotein transport. For an excellent, more detailed review of the transport of triglyceride-rich lipoproteins, the reader is referred elsewhere.[8]

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PHYSIOLOGY OF NORMAL PLASMA LIPID TRANSPORT

Triglyceride and cholesterol, the two circulating lipids which have been shown to correlate with atherosclerotic disease when present in high concentration, circulate in plasma in close association with protein (apoproteins) and phospholipid, which serve both to solubilize the lipids and provide a vehicle for transport. Each apoprotein appears to have a specific capacity to accommodate all the major plasma lipids in varying proportions. The protein and lipid content of each lipoprotein determines its size, density, and electrophoretic migration (Fig. 1). These physical properties provide a basis for their ultracentrifugal and electrophoretic separation.

The largest of the lipid-protein aggregates is the chylomicron (Fig. 1), which is formed in the intestinal mucosa during the process of absorption of dietary fat. Because of its large size, the chylomicron scatters transmitted light, and hence when present in plasma in even relatively small concentrations may cause visible turbidity or lactescence. Chylomicrons are not normally present in plasma after an overnight fast. Because of their very high triglyceride (>90 per cent) and low protein (2 per cent by weight) content, they are the least dense of the lipoproteins. The more dense lipoproteins contain relatively more protein than lipid. The large size of the chylomicron is responsible for its lack of electrophoretic mobility on some media (e.g., paper).

Another source of triglyceride-rich lipoproteins in plasma is the liver (Fig. 2). Since lipoproteins of hepatic origin contain less triglyceride and

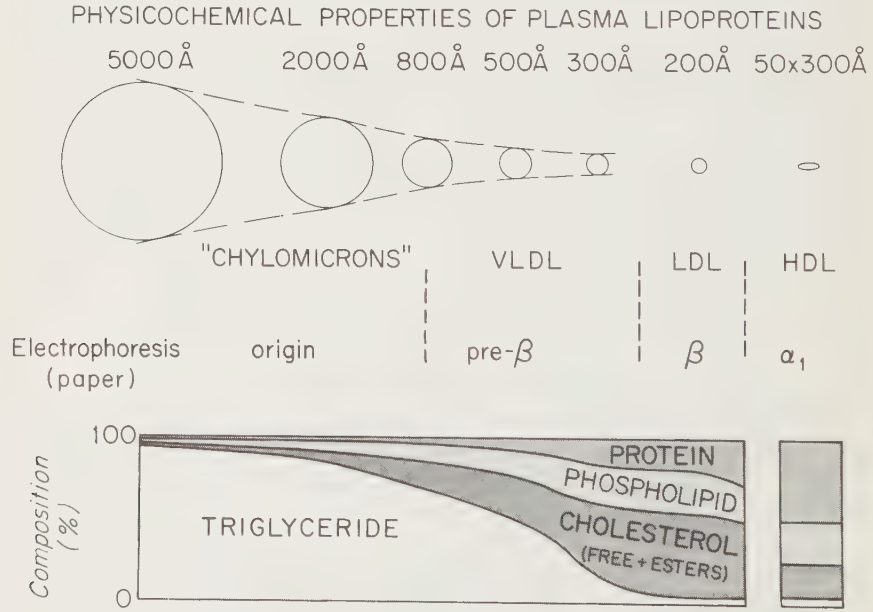

Figure 1. Relationship between lipoprotein size, electrophoretic migration on paper, and composition.

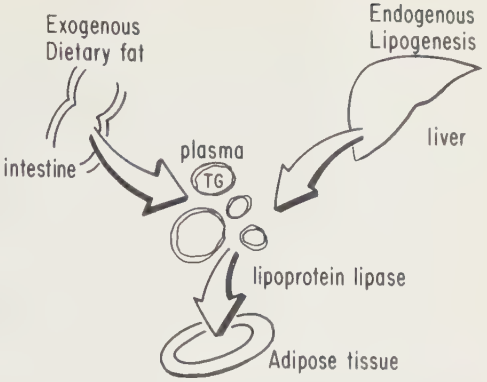

Figure 2. Sources of circulating plasma triglyceride-rich lipoproteins and their common removal mechanism.

relatively more protein, cholesterol, and phospholipid, they are smaller and slightly more dense than chylomicrons. Because of their density and ability to move off the origin on most types of lipoprotein electrophoresis, and on paper electrophoresis migrate ahead of the beta-globulins, they are referred to as the "pre-beta" or alpha-2 lipoproteins, or in the terminology of the ultracentrifuge, "very low density" lipoproteins (VLDL).

The pre-beta lipoproteins also may become large enough to scatter light and cause plasma lactescence when present in high concentration. In contrast to chylomicrons, however, these lipoproteins are always present in plasma in the fasting state. Since their production and secretion into plasma appears to be increased normally by weight gain, alcohol, and increased carbohydrate intake, abnormalities in this lipoprotein class are frequently encountered in American males during the middle decades of life when relatively increased ingestion of calories, alcohol, and carbohydrate all commonly take place.

Since these lipoproteins contain significant amounts of cholesterol (15 to 30 per cent), the total plasma cholesterol concentration will be increased in proportion to the VLDL elevation in states in which VLDL accumulate abnormally. This increase in cholesterol should not be mistakenly interpreted as evidence of any abnormality in the cholesterol-rich beta-lipoprotein class.

The lipoprotein lipase enzyme system (Fig. 2) appears to mediate the tissue removal of triglyceride-rich lipoproteins of both dietary and endogenous origin, and from its location near the surface of capillary endothelium of adipose and other tissues, it plays a key role in the hydrolysis and assimilation of circulating triglycerides from plasma. This enzyme may be estimated indirectly by the measurement of lipolytic activity in plasma following intravenous administration of heparin (post-heparin lipolytic activity or PHLA), which releases the enzyme into the circulation. The PHLA is commonly used as an index of triglyceride-removal capacity.

The cholesterol-rich beta-lipoproteins, so called because they migrate with the beta-globulins on electrophoresis, are 50 per cent cholesterol by weight and carry one-half to two-thirds of the total plasma cholesterol in normal subjects. Because they contain relatively more

protein, they are more dense then the triglyceride-rich lipoproteins, and hence are called low-density lipoproteins (LDL). Since LDL also contain small amounts of triglyceride (Fig. 1), in clinical states in which beta-lipoprotein concentrations are markedly elevated the total plasma triglyceride also may reach abnormal levels. This should not be interpreted as evidence of a primary abnormality in the transport of triglyceride-rich lipoproteins.

The precise biologic function of beta-lipoprotein is unclear. Its site of synthesis in both intestinal and hepatic cells and the effects of its absence in abetalipoproteinemia suggests that its peptide portion may be essential for the transport of triglyceride. Beta-lipoprotein concentrations are normally maintained within a narrow range, and in contrast to VLDL are not influenced by caloric balance and usually are only slightly affected by dietary alteration.

DIAGNOSTIC TESTS FOR HYPERLIPOPROTEINEMIA

Advances in methodology have been responsible for recent progress in our understanding of the disorders of lipid transport. Information derived from the appearance and measurement of the serum or plasma triglyceride and cholesterol levels, coupled with knowledge of the electrophoretic distribution of the plasma lipoproteins which can be obtained with relatively simple and inexpensive techniques, now make it possible to characterize correctly most abnormalities of lipid transport, when placed in the context of the complete clinical picture.

APPEARANCE OF PLASMA. The appearance of plasma obtained after an overnight fast may yield valuable information regarding the presence of an underlying lipoprotein abnormality. The formation of a cream layer atop fresh plasma after centrifugation or a brief period of refrigeration *always* indicates the presence of chylomicrons, a finding which usually indicates some abnormality in triglyceride removal. Because of their large size and ability to scatter light, relatively small numbers of chylomicrons can cause lactescence. Their smaller size and lower triglyceride content may explain why relatively high VLDL concentrations must be present in plasma before turbidity appears (Fig. 1) and no cream layer forms.

From a practical point of view, completely clear plasma or serum suggests that the plasma triglyceride level is normal and rules out disorders of chylomicron and VLDL transport. In contrast, very high levels of beta-lipoprotein may accumulate without any alteration in turbidity, since these smaller more dense lipoproteins do not scatter transmitted light. Thus hyper-beta-lipoproteinemia is the only common clearly defined disorder of lipoprotein transport in which the serum is characteristically non-lactescent. All other recognized varieties of hyperlipoproteinemia are manifested by varying degrees of hyperlipemia or lactescent plasma.

PLASMA LIPID MEASUREMENTS. The diagnosis of a specific plasma lipoprotein abnormality cannot be established on the basis of an ab-

normal concentration of either triglyceride or cholesterol. However, both measurements together may point to the accumulation of a particular lipoprotein. For example, a markedly increased plasma triglyceride level associated with a normal or only slightly increased cholesterol concentration reflects the composition and probable accumulation of chylomicrons. The proportional increase of both triglyceride and cholesterol levels suggests VLDL accumulation. A cholesterol elevation associated with a normal triglyceride concentration indicates an abnormality in the beta-lipoprotein class.

Lipoprotein Electrophoresis. The technique of electrophoretic separation of lipoproteins, employing a variety of supporting media such as paper, agarose gel, polyacrylamide gel and cellulose acetate, has added a new and conveniently obtained dimension to our understanding of the disorders of lipid transport. Employing paper strip electrophoresis, investigators at the National Institutes of Health have defined five distinct types of abnormal lipoprotein patterns in plasma. These will be discussed in detail subsequently.

PHYSICAL FINDINGS IN HYPERLIPOPROTEINEMIA

While the precise mechanism whereby circulating lipoproteins deposit in arterial intima is still controversial, recent studies[13] have shown that transport of lipoprotein from plasma to skin occurs frequently in various disorders of lipid transport, the type and distribution of the skin lesions varying with each specific lipoprotein.

Eruptive xanthomas typically appear on the buttocks, elbows, and knees of patients with any one of the several conditions in which chylomicrons accumulate (Figs. 3, 4). The chemical composition of these

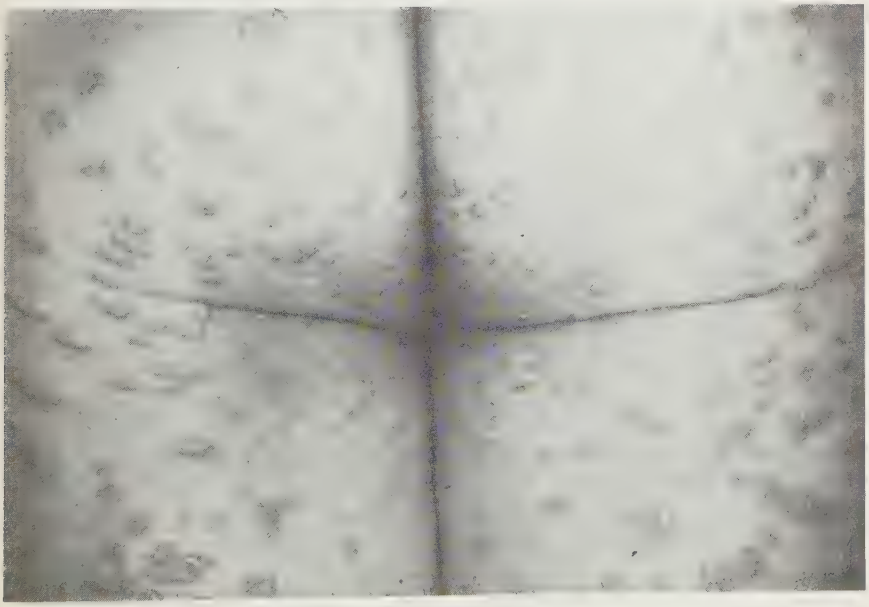

Figure 3. Eruptive xanthoma involving buttocks in patient with chylomicronemia.

papular lesions which have a characteristic erythematous halo is identical to that of the circulating chylomicron.[12] Following treatment of the underlying disorder and disappearance of the chylomicronemia, these lesions regress.

Xanthelasma frequently indicate an abnormality in the cholesterol-rich beta-lipoprotein class (Fig. 5). In addition to their well known propensity to accumulate in the coronary vessels, these lipoproteins also deposit in tendons, typically causing an irregular thickening of the Achilles and extensor forearm tendons (Fig. 6).

Figure 4. Eruptive xanthoma involving the elbow in patient with chylomicronemia.

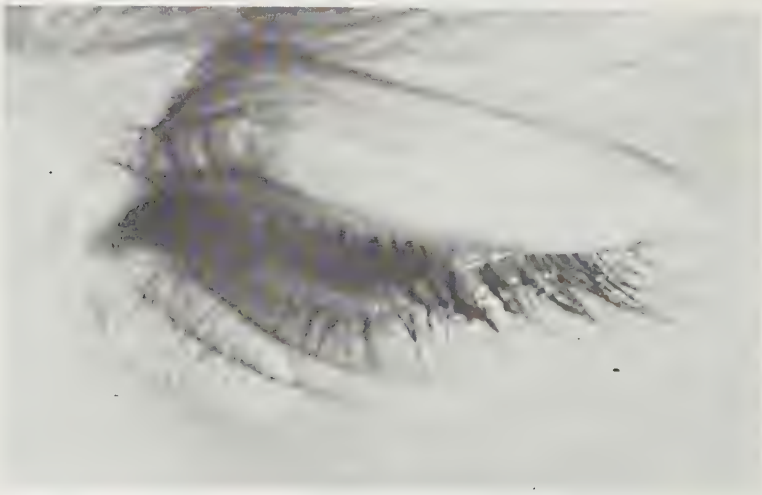

Figure 5. Prominent xanthelasma of eyelids in patient with hyperbetalipoproteinemia. These lesions may appear in patients with both familial and acquired forms of this disorder.

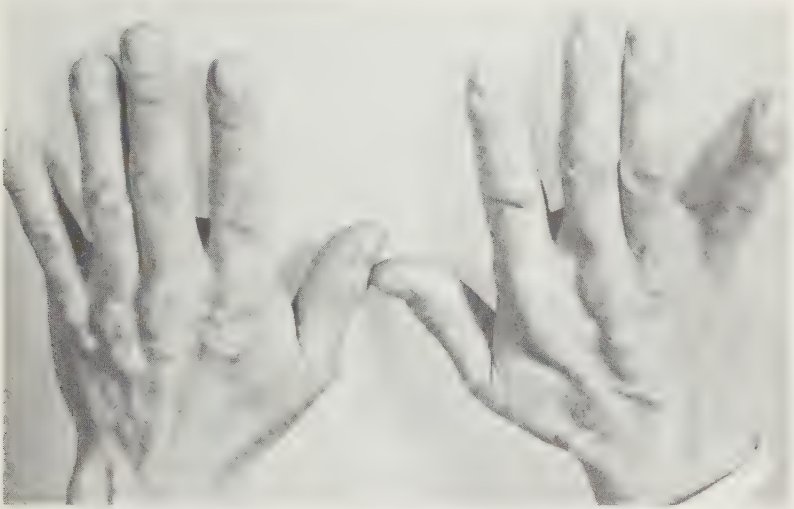

Figure 6. Thickened extensor tendons in patient with familial hyperbetalipoproteinemia.

Figure 7. Prominent planar xanthoma in a patient with broad-beta lipoprotein disease.

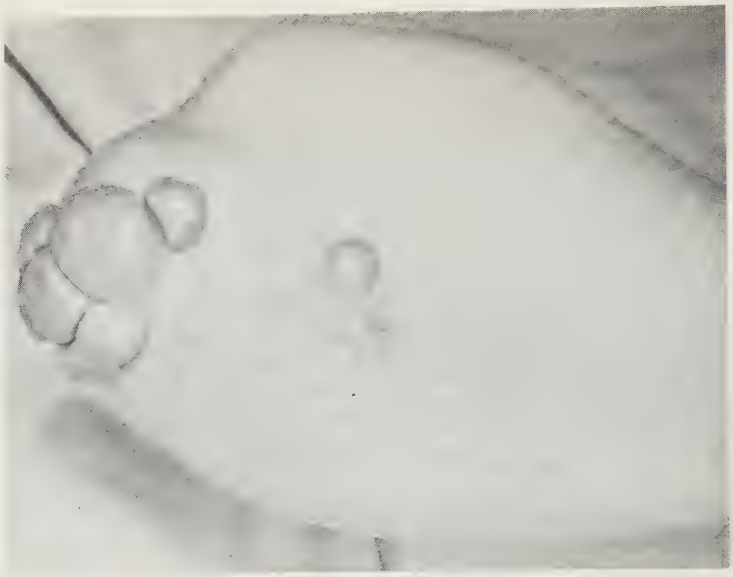

Figure 8. Tuberous xanthoma involving the elbow of a patient with broad-beta lipoprotein disease.

Planar xanthoma involving the palms and soles and tuberous xanthoma of elbows and knees may appear when a distinctive cholesterol-rich VLDL accumulates in broad-beta disease (Figs. 7, 8).

PRIMARY AND SECONDARY HYPERLIPOPROTEINEMIAS

In contrast to chylomicronemia, which appears to result from a specific defect in the transport of exogenous (dietary) fat, the beta, broad-beta, and pre-beta lipoproteins which are produced de novo in the body also may accumulate in plasma. The mechanisms contributing to these abnormalities are not at all clear,[12] but the accumulation of each lipoprotein appears to reflect a specific defect of lipoprotein regulation with distinctive clinical features, and dietary therapy. Since all forms of endogenous hyperlipoproteinemia predispose to premature atherosclerosis, these disorders should be considered in any young patient with cardiovascular disease.

Hyperbetalipoproteinemia

Familial hyperbetalipoproteinemia is a serious disease, resulting presumably from delayed catabolism of beta lipoprotein.[10] Cardiovascular complications believed to result from persistent elevation of this cholesterol-rich lipoprotein class are frequent. In the unfortunate patient with the homozygous form of this autosomal dominant disease, tendinous xanthomas (Fig. 6) typically appear during the first decade of life, and death from coronary atherosclerosis occurs prematurely.

Diagnosis is suggested by history, the typical physical findings of

tendon xanthomas, xanthelasma, corneal arcus, elevated plasma cholesterol levels, and a discrete, intensely staining beta band on lipoprotein electrophoresis (Type II pattern). Since the beta-lipoprotein contains relatively more protein and less triglyceride than the larger VLDL, its capacity to scatter light and cause turbidity is limited. Hence, plasma in the patient with beta-lipoprotein elevation is clear (Table 1).

As with other inborn errors of metabolism, genetic expression may vary considerably. Some heterozygotes may demonstrate increased beta-lipoprotein levels alone, without cardiovascular complications. Detection of the heterozygote and children of affected parents requires the same battery of routine diagnostic studies. Beta-lipoprotein elevation also may occur secondarily in hypothyroidism, in which the removal rate is presumably decreased;[17] in nephrosis, in which production may be increased; and occasionally in patients with myeloma or macroglobulinemia, in whom an abnormal globulin is believed to bind to beta-lipoprotein and diminish its clearance rate.[15] A Type II pattern also is frequently encountered in patients with obstructive liver disease and may be found as well in patients who have ingested excessive amounts of dietary cholesterol or saturated fat. These secondary causes for beta-lipoprotein elevation can usually be ruled out by thyroid, renal and hepatic function tests, protein electrophoresis, and dietary history.

Dietary Therapy. Dietary treatment offers the safest and most effective long-range program for both the prevention and the treatment of hypercholesterolemia.[4] Decreasing the dietary cholesterol intake from the average daily American consumption of 750 mg. per day to 50 to 100 mg. daily is an essential step in therapy, since cholesterol of dietary origin will accumulate beyond the ability of the body to reduce the amount synthesized in the liver and intestine from endogenous precursors. About a 25 per cent reduction in beta-lipoprotein cholesterol may be anticipated by significantly reducing cholesterol intake. Total plasma cholesterol levels may not change in some patients on low-cholesterol diets, since isocaloric substitution of carbohydrate for the calories formerly derived from fat may stimulate production of cholesterol-containing VLDL.

The substitution of polyunsaturated fats such as corn, cottonseed, safflower and soy oils for saturated fat offers an additional dietary means of successfully lowering beta-lipoprotein cholesterol levels. In addition to inducing a state of negative cholesterol balance, the polyunsaturates appear to lower cholesterol by altering the spatial configuration of lipid-protein associations.[16] The net effect of this steric alteration of the cholesterol ester molecule, induced by placing an unsaturated fatty acid on the sterol ring, is to decrease the number of cholesterol molecules which can be accommodated on the carrier beta-lipoprotein. Prospective studies to determine whether these dietary modifications indeed alter survival and prevalence of cardiovascular disease are currently in progress. A further reduction in beta-lipoprotein levels may be achieved with supplemental drug therapy (Table 2).

Endogenous Hypertriglyceridemia (Hyperprebetalipoproteinemia)

In the normal postabsorptive state, the liver secretes a small but con-

Table 1. *Characteristic Alterations in Hyperlipoproteinemic States*

CLASS PREDOMINANTLY ELEVATED	ELECTROPHORETIC PATTERN	PLASMA APPEARANCE	PLASMA TRIGLYCERIDE	CHOLESTEROL	XANTHOMAS (WHEN PRESENT)
Chylomicrons (S_f 400) (VLDL)	Origin (I)	Milky	↑ ↑ ↑	±	Eruptive
Low density lipoproteins (S_f 0–20)	beta (II)	Clear (xanthochromic)	normal –	↑ ↑ ↑	Tendinous
VLDL (esp. S_f 20–100)	Broad-beta (III)	Turbid	↑ ↑	↑ ↑	Tuberous, Palmar planar
VLDL (S_f 20–400)	pre-beta (IV)	Turbid	↑ ↑	normal or ↑	–
Chylomicrons + VLDL	Origin and pre-beta bands (V)	Turbid-milky	↑ ↑ ↑	↑	Eruptive

Table 2. *Treatment of Familial Hyperlipoproteinemias*

DISORDER	DIETARY THERAPY	DRUG THERAPY
Exogenous lipemia (fat-induced lipemia, hyperchylomicronemia, Type I)	Fat restriction (Add medium-chain triglyceride)	None
Familial hypercholesterolemia, hyperbetalipoproteinemia (Type II)	Restriction of dietary cholesterol and saturated fats	1. Cholestyramine (investigational) 2. Nicotinic acid 3. D-thyroxine
Broad-beta disease, dysbetalipoproteinemia (Type III)	Weight reduction Restriction of dietary cholesterol and saturated fats	1. Clofibrate 2. Nicotinic acid
Endogenous lipemia (Type IV) (carbohydrate-induced lipemia, hyperprebetalipoproteinemia)	Weight reduction	1. Clofibrate 2. Nicotinic acid 3. Phenformin
Mixed lipemia (Type V)	Weight reduction	1. Clofibrate 2. Nicotinic acid 3. Progesterone

stant amount of triglyceride-rich lipoprotein into the circulation. Production of this pre-beta migrating VLDL is normally increased by weight gain, alcohol, a high-carbohydrate diet, and probably also by drugs such as estrogen and corticosteroids. The primary demonstrable defect in patients with the familial or sporadic form of endogenous hypertriglyceridemia is an abnormal accumulation of pre-beta migrating VLDL in the absence of any of these known stimuli (Type IV).

Because of the markedly elevated triglyceride levels observed in these patients in response to high-carbohydrate fat-free diets, it was formerly believed that their metabolic defect was related specifically to carbohydrate, and hence was referred to as "carbohydrate-induced" lipemia. Since non-lipemic subjects also normally double basal triglyceride levels in response to fat-free diets,[3] it is now quite clear that "carbohydrate-induction" is a normal phenomenon. The distinguishing feature in patients with endogenous lipemia is abnormal VLDL regulation in the basal state with ingestion of normal amounts of carbohydrate and fat.

The familial form of this disorder appears to be transmitted as an autosomal dominant trait with delayed expression.[5] Because of its frequent occurrence and high incidence of associated premature coronary atherosclerosis, this disorder should be considered in any young patient with heart disease. Basal triglyceride levels are characteristically elevated. Since the VLDL which accumulates in this disorder contains significant amounts of cholesterol, total serum or plasma cholesterol levels also may be increased (Table 1).

While the majority of these patients are obese and demonstrate glucose intolerance, many are non-obese and have normal carbohydrate tolerance. Identical abnormalities in the VLDL and a Type IV lipoprotein electrophoretic pattern may occur during weight gain, and secondarily

in alcoholism, hypothyroidism, the nephrotic syndrome, dysglobulinemia, pregnancy, uremia, and in patients receiving estrogen-containing preparations. It has been suggested that obesity is one factor which may commonly unmask an underlying abnormality in VLDL production in affected individuals,[3] in a manner similar to the deleterious effects of obesity on carbohydrate tolerance.

DIETARY THERAPY. Since obesity and caloric balance clearly exert a profound influence on VLDL production, dietary therapy is essential in patients with endogenous hypertriglyceridemia. Vigorous efforts should be made in the overweight patient to achieve ideal body weight through caloric restriction. As long as the prescribed diet is hypocaloric, the actual carbohydrate content is not important, since hepatic VLDL production is not increased by carbohydrate in states of negative caloric balance.[14] In many patients weight loss alone results in the restoration of normal triglyceride levels. If hypertriglyceridemia persists after ideal weight is achieved, modest carbohydrate restriction is indicated. Practically speaking, this regimen merely restricts the use of excessive carbohydrate calories. While dietary therapy is the far more effective form of treatment, clofibrate (Atromid-S) may be added in patients who cannot adhere to the dietary regimen (Table 2).

There is no rationale for restricting dietary fat in non-obese patients with endogenous hypertriglyceridemia; some degree of fat restriction, however, is a useful part of any weight-reducing regimen. Since alcohol may increase VLDL production both by altering the caloric balance and directly stimulating hepatic synthesis, alcohol intake should be eliminated in patients with any abnormality in VLDL transport.

Exogenous Hyperlipemia (Hyperchylomicronemia)

When the lipoprotein lipase enzyme system is deficient and the normal removal of both chylomicrons and presumably VLDL from plasma is impaired, a distinctive clinical syndrome characterized by abdominal pain, hepatosplenomegaly, lipemia retinalis, and eruptive xanthoma may develop. Lipoprotein lipase reduction may be seen occasionally in its congenital (recessive transmission) form; however, it is more frequently encountered when acquired, commonly in poorly controlled diabetes mellitus.[1] In either case, persistent chylomicronemia appears to contribute directly to each clinical feature. The diagnosis may be confirmed by detecting subnormal lipoprotein lipase activity in post-heparin plasma, chylomicronemia after an overnight (12 hr.) fast, and markedly elevated plasma triglyceride with normal or only slightly increased cholesterol levels. Lipoprotein electrophoresis typically shows chylomicron accumulation, normal or even reduced alpha and beta lipoprotein bands, and usually some pre-beta migrating lipid (Type I; Table 1).

DIETARY THERAPY. No matter what the cause, elimination of dietary fat lowers the circulating plasma lipids to near normal levels, since chylomicron input is sharply reduced. Consequently, in cases of congenital lipoprotein lipase deficiency, reduction of fat intake to 30 gm. or less daily is essential. It is possible, however, particularly in children in whom fat ingestion provides admirably for the considerable

caloric demands of growth, to take advantage of the fact that medium chain length (less than 12 carbon atoms) fatty acids pass directly from the intestinal absorptive cell directly into the portal vein without chylomicron formation. Thus, feeding medium-chain triglycerides may be employed as a means of providing fat calories in patients who do not tolerate the usual forms of dietary fat.

When altered lipoprotein lipase function is secondary to other disorders such as poorly controlled diabetes mellitus, hypothyroidism, or occasionally a dysgammaglobulinemia such as myeloma, lymphoma, or lupus, successful treatment of the underlying disorder is followed by disappearance of chylomicronemia and normalization of lipid levels.

Mixed Hyperlipoproteinemia

When triglyceride-rich fat particles of both dietary and endogenous origin accumulate simultaneously, post-absorptive plasma is lactescent, and plasma triglyceride and cholesterol levels are both increased. Patients in whom chylomicrons and increased amounts of endogenously synthesized pre-beta lipoprotein are demonstrable on lipoprotein electrophoresis have been classified as having Type V or mixed hyperlipoproteinemia (Table 1). Similar to the other lipoprotein electrophoretic abnormalities, this pattern may result from primary (familial or sporadic) or acquired disorders.

Only the occasional patient with a Type V pattern will be found to have the inherited form (autosomal dominant). More commonly this pattern will be encountered in patients with diabetes mellitus, alcoholic pancreatitis, and nephrosis. The rare patients with glycogen storage disease or congenital lipodystrophy also may demonstrate a mixed form of lipemia and a Type V pattern. Whatever the underlying cause, when chylomicronemia is marked, a clinical picture identical to that observed in exogenous lipemia, with abdominal pain, hepatosplenomegaly, lipemia retinalis, and eruptive xanthoma, may develop.

The clinical similarity between disorders associated with Type I and Type V electrophoretic patterns has led to the speculation that function of the lipoprotein lipase enzyme system may be impaired in patients with mixed lipemia, despite normal post-heparin lipolytic activity. Endogenous VLDL production may be so markedly increased, and plasma VLDL levels so high in some patients with endogenous lipemia, that the maximal triglyceride removal capacity of tissues may be exceeded. Since chylomicrons and endogenously synthesized VLDL are presumed to share a common removal mechanism, the addition of dietary fat particles to such patients' already expanded triglyceride pool might be expected to result in chylomicron accumulation. Consequently, some patients with endogenous hypertriglyceridemia may demonstrate a Type V electrophoretic pattern.

The patient with endogenous hypertriglyceridemia and a Type IV pattern also may develop chylomicronemia and acquire a Type V pattern, with deterioration of glucose tolerance as insulin availability diminishes and function of the insulin-dependent enzyme lipoprotein lipase decreases. Such a transition may occur when fasting glucose levels exceed 150 mg. per 100 ml.[2] In such patients, diabetic treatment abolishes the

chylomicronemia and restores the Type IV pattern. The patient who develops a Type V pattern during bouts of heavy ethanol ingestion or acute pancreatitis also is likely to have an underlying primary abnormality in lipoprotein transport.[7] Most patients with alcoholic pancreatitis demonstrate only mild increases in the plasma lipids.

DIETARY THERAPY. In the more commonly encountered patients with mixed lipemia and a Type V electrophoretic pattern associated with diabetes or alcohol, treatment of the underlying disease usually eliminates the chylomicronemia and restores the underlying endogenous hypertriglyceridemia picture. Therapy as outlined in the discussion of endogenous lipemia should be followed (Table 2). In the relatively uncommon patient with the familial form of mixed hyperlipoproteinemia, reduction to ideal body weight is essential. If plasma lipids remain above normal after reduction to ideal body weight, some restriction in dietary carbohydrate and fat is indicated, and drug therapy with clofibrate (Atromid-S) or progesterone[6] may be useful.

Broad-Beta Disease (Dysbetalipoproteinemia)

This unique disorder is the least common of the familial diseases of lipoprotein transport, but shares with them the predisposition to premature atherosclerosis of both the coronary and the peripheral vessels. Clinically, these patients develop characteristic planar xanthomas of the skin creases and particularly the palms, but they also may demonstrate tuberous (Fig. 7) and eruptive xanthomas as well. This is the only lipoprotein disorder in which planar xanthomas are found; hence, their presence should immediately suggest this diagnosis.

Plasma triglyceride and cholesterol levels are both increased in this disease, usually in equal proportions. The mechanism for the accumulation of this unique cholesterol-rich VLDL which migrates electrophoretically in between the normal beta and pre-beta position on paper or agarose gel electrophoresis is unknown. An associated abnormality in the catabolism of chylomicrons is suggested by the presence of cholesterol-rich chylomicrons in the plasma of these patients after an overnight fast.[9]

The clinical findings, approximately equally increased plasma triglyceride and cholesterol levels, and a broad-beta electrophoretic pattern (Type III), strongly suggest this diagnosis. However, preparative ultracentrifugation and VLDL compositional analysis usually is required to establish the diagnosis, particularly in asymptomatic but affected family members.[9] This abnormal lipoprotein has not been associated with any other disease. Inheritance appears to follow an autosomal recessive pattern.

DIETARY THERAPY. Since production of this abnormal lipoprotein appears to be exquisitely sensitive to both caloric balance and dietary cholesterol intake, dietary therapy is an essential part of any attempt to normalize the plasma lipids in this disorder. Weight reduction should be recommended for any overweight patient because it drastically reduces endogenous VLDL production. Efforts should be made to achieve ideal body weight in all patients with broad-beta disease. When ideal body weight is reached, a low cholesterol, low saturated fat diet balanced in

carbohydrate and fat is frequently sufficient to maintain normal lipid levels.[11] In patients in whom weight reduction cannot be realized or in whom lipid levels remain elevated, clofibrate (Atromid-S) may be added to the diet (Table 2).

CONCLUSIONS

A detailed medical history, with particular attention to the familial occurrence of premature cardiovascular disease, and a careful physical examination form an essential part of the clinical evaluation of any patient with hyperlipoproteinemia. A few simple and inexpensive laboratory tests may be employed to detect an abnormality in the circulating serum lipoproteins. In general, these hyperlipoproteinemic states may result from: (1) an impaired capacity to normally remove circulating lipoprotein from the circulation, a situation in which dietary fat (chylomicrons) accumulates and the appearance of plasma after an overnight fast is typically turbid; (2) an increased rate of hepatic production of triglyceride-rich lipoproteins which exceeds the removal capacity of peripheral tissues; (3) a combination of these abnormalities.

While it has been possible thus far to identify at least five distinctive abnormalities by lipoprotein electrophoresis in patients with familial disorders of lipid transport, identical electrophoretic patterns may be acquired in patients with a variety of altered metabolic states, and may not have the same diagnostic or prognostic significance as in patients with familial disorders. When serum lipoprotein abnormalities are acquired, they typically disappear following treatment of the underlying disorder. Specific therapy designed to lower lipid levels should be reserved for the patient with no evidence for a secondary cause for hyperlipoproteinemia and a persistently abnormal increase in serum lipids. Dietary treatment is an essential part of the therapy of each of the clearcut familial disorders of lipid transport. The type of dietary treatment prescribed will be determined by the specific lipoprotein abnormality.

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Current Concepts of Iron Metabolism and the Iron Deficiency Anemias

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The deficiency of iron, nature's most abundant metal, ranks as the most common of nutritional deficiencies in the human. Unexpectedly, this is true not only in underdeveloped countries such as India, but in the United States as well. Iron deficiency anemia, at some point during the first 2 years of life for some American children, is the rule rather than the exception,[1] with some surveys reporting an incidence as high as 64 per cent in this group.[47]

The subsequent harm done by the transient deficiency of iron during infancy is obviously difficult to isolate and measure experimentally, because of the multitude of other nutritional requirements and cultural factors that also play a crucial role in child development.[45] A number of studies,[12, 45, 46] however, point to early nutritional lack impairing not only physical growth but intellectual development as well. Thus the learning difficulties seen in many underprivileged children in whom iron deficiency during infancy is so common may be in part the price paid for this early period of deprivation.

Because of the stresses placed on iron balance by menstruation and pregnancy, women of child-bearing age are frequently found to be anemic[2] or incipiently deficient on the basis of reduced or depleted body iron stores.[33] Iron deficiency in the adult American male, though less common than in the pregnant woman or in infants, is almost always due to pathologic blood loss. The clinician should recognize this most important signal of underlying disease, frequently a lower bowel carcinoma, and pursue the primary diagnosis until found.

From the standpoint of correcting these deficiencies, the goal is uniform—the repletion of functional and storage iron by the administration of iron supplements. With respect to the diagnosis and a rational approach to the treatment of the deficiency state, an understanding of some of the fundamental aspects of iron biochemistry, physiology, and nutrition is essential and will be reviewed.

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IRON METABOLISM

Biochemistry

Iron is one of the most versatile metals, in that its atomic structure lends itself to performing a wide range of biochemical activities.[15] Having two oxidation states, the more stable Fe^{+3} (ferric) and the Fe^{+2} (ferrous) forms, it is able to catalyze the oxidation/reduction reactions involved in electron transport. Both heme and non-heme iron are involved in these processes[18] which are fundamental to the organism's utilization of oxygen for the formation of high-energy phosphate bonds and are found throughout nature in practically all oxygen utilizing organisms.

Additionally, iron can form six covalent bonds, four of which serve

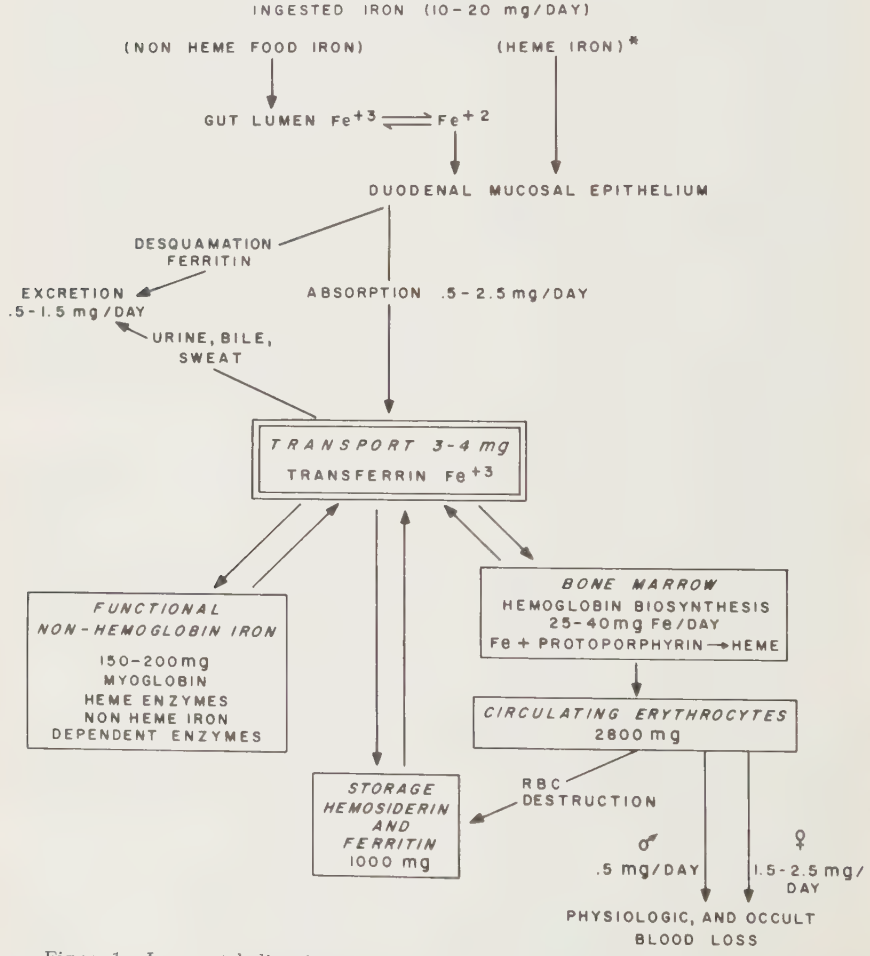

Figure 1. Iron metabolism in a 70 kg. adult. *Heme iron absorption occurs by a mechanism different from that of other iron compounds.

to bind the metal to the porphyrin ring to form heme. One of the two remaining coordinating positions of iron helps bind the heme to a histidine residue of globin, the protein portion of hemoglobin; and the other serves (with Fe in the ferrous state) to reversibly bind molecular oxygen, the basic role of this heme protein.[19]

Many enzymes require non-heme iron such as aconitase and succinic dehydrogenase of the Krebs tricarboxylic acid cycle, as well as a number of flavin and pyridine-linked oxido-reductases.[18]

Thus, although anemia is the most common and most readily appreciated clinical finding accompanying iron lack, it is not surprising that functions other than just oxygen transport are impaired. Beutler[3] has shown in animals, that following experimentally induced iron deficiency tissue activity of the iron-containing or iron-dependent enzymes (e.g., cytochrome oxidase) cytochrome C, succinic dehydrogenase, and aconitase is reduced. The precise relationship between the reduction in one or more tissue enzyme activities in human iron deficiency and the associated symptoms is, however, less clear cut.

Distribution of Body Iron

The total amount of iron in a healthy 70 kg. adult male amounts to 3.5 to 4.5 gm. As would be expected of so biologically active a metal, virtually all of this iron is bound to protein, either as functional iron, such as in hemoglobin and the iron-requiring enzymes, or as storage or transport iron.

As shown in Table 1, most of this iron is present in the form of hemoglobin, constituting from 65 to 70 per cent of the total. By weight, hemoglobin contains 0.34 per cent iron, or 3.4 mg. Fe per gm.; thus at a hemoglobin concentration of 15 gm. per 100 ml., 1 ml. of whole blood would contain 0.5 mg. of iron. The daily loss of 20 ml. of blood from an obscure lesion of the gastrointestinal tract would therefore result in an iron loss of about 10 mg. per day. Appreciating these relationships, one can readily see how in a fairly short period of time, perhaps 3 to 4 months, body iron stores would become depleted as a result of this relatively minor degree of bleeding. Most of the remainder (20 to 25 per cent) of body iron is found in the ferric form in the reticuloendothelial

Table 1. *Distribution of Body Iron*

	IRON (MG.)		TOTAL BODY IRON (%)	
COMPOUND	70 kg. Male	3.0 kg. Newborn	Adult Male	Newborn
Hemoglobin	2,800	156	65–70	70–75
Tissue Iron	150	21	4	10
Myoglobin				
Enzymes				
Storage	1,000	20–30	20–30	10–15
Transport	3–4	< 1	< 1	< 1
Total	3,500–4,500	200–225		

system in storage proteins,[43] these being water-soluble ferritin and the less soluble storage molecule hemosiderin, which is thought to be a breakdown product of ferritin.[20] Functional nonhemoglobin iron, including myoglobin and enzyme iron as well as the iron in transport bound to transferrin, account for less than 5 per cent of the adult's total supply.

At birth, a somewhat greater proportion of the iron with which the infant is endowed is in the form of red cell hemoglobin (70 to 75 per cent) with tissue stores of the metal usually amounting to less than 25 mg., or about 15 per cent of the total.[38] With this in view, then, it is not difficult to understand why infants who triple their birth weight during their first year of life (and appreciably enlarge their hemoglobin mass) are prone to developing iron deficiency,[41] especially if nutrients other than milk, a notoriously poor source of iron, are not consumed in sufficient amounts during this crucial period of development.[45]

Iron Absorption

A number of very elegant studies[30, 39, 44] using radioactive inorganic iron added to food as well as naturally labeled food iron have served to elucidate some of the factors that influence iron absorption. As is the case with many complex physiologic processes, new knowledge has brought into focus additional unknowns, and the relative importance of many of the findings to the overall process of intestinal iron absorption is far from settled.[13, 25]

A detailed account of the many factors that normally influence iron absorption is beyond the scope of this review; however, in brief, they fall under three major headings. The endogenous factors would include the status of iron nutrition, erythropoietic activity, and the hemoglobin level.[6] Among the gut or luminal factors that influence this process are pancreatic secretions and gastric secretory factors, in addition to hydrochloric acid. Other factors such as gut transit time, mobility, and digestive capacity also play a role. Lastly, food or exogenous factors also heavily influence the amount of iron absorbed.[23, 31] This varies with respect to the iron content of food and the various molecular forms of iron found in foods, as well as the chemical properties of food per se. Some foods such as orange juice[9] appear to enhance iron uptake, probably owing to the presence of ascorbic acid, while others such as wheat, which contain phytates, appear to retard this process.[30] Potent iron chelators such as deferoxamine (Desferal) also have been shown to be capable of reducing food iron absorption.[24, 30]

The major site at which the physiologic control of iron absorption occurs is the duodenal epithelium. Animal experiments[11] have shown that a variable amount of iron absorbed at this site is transferred to the plasma iron-binding protein, transferrin, and the remainder of that taken up by the cell remains within the cell in the form of ferritin. Thus, in the case of iron deficiency, most of the iron is taken up by the plasma, whereas in the presence of normal iron stores or iron overload much of the iron remains in the cell as ferritin. Inherent in the design of such a system is the enhancement of iron loss in the face of iron repletion or overload by way of epithelial desquamation and diminished losses of the metal during periods of deficiency (Fig. 1).

Although it is well established that iron deficiency acts as a potent stimulus to the absorption of inorganic and food iron, recent studies of iron deficient children and dogs indicate that iron lack at the tissue level may also impair iron absorption as a result of biochemical derangements of the absorbing epithelium.[28] This may be somewhat akin to the occurrence of malabsorption of folate and B_{12} in the presence of a deficiency of these vitamins.[10, 42]

FOOD IRON

Availability of Food Iron

The average daily American diet contains from 9 to 18 mg. of iron.[30, 51] This varies considerably, not only with the quantity and type of food consumed but also with respect to the manner in which food is processed and cooked.[29] Calculated on the basis of mg. of iron per 1,000 calories of food consumed, values for the calculated and analyzed iron content of the average American diet range from 6 to 8.5 mg. per 1000 calories respectively. It is of interest to note that the current diminishing popularity of iron cookware in favor of aluminum and enameled pans, as well as the more refined present day methods of food processing, have probably served to decrease the overall daily intake of iron in today's American diet.

A few representative foods, with their iron contents and respective absorbabilities in normal as well as deficient subjects, are presented in Table 2. The range of per cent absorption for most is very wide; however, it will be noted that in all instances, absorption is increased by the deficiency state. Since few meals actually consist of only a single item,

Table 2. *Absorption of Iron from Various Sources*

SOURCE	IRON CONSUMED (MG.)	IRON ABSORBED (%)	
		Normals	Iron-Deficient Adults
Whole wheat bread,[16] Iron-enriched	0.06	1.4	–
Black beans[31]	3–4	2.3	7
Corn[31]	3–4	2.1	7.9
Veal muscle[31]	4	20.2	27.1
Fish[31]	1	6	–
Egg[35]	2	3	9
Lettuce, spinach[35]		3	9
Liver[35]		8	22
Hemoglobin (raw)[8]	5	10	22
Hemoglobin (cooked)[8]	5	7	12
Standard meal[39]	4.6	5.3	21.6
Ferrous sulfate[6] +1 gm. vitamin C	1–2 mg./kg.	6.1–16	37.5
Ferrous sulfate alone[6]	1–2 mg./kg.	8.2–12	
Wine[32]	3–4 mg./liter	(15) estimated	–
Milk[34]	0.5–1.5 mg./liter	9	16 (infants)

the overall absorbability of the iron contained in a standard meal has also been investigated.[39] This averages about 5 per cent in normals and rises some four-fold in the presence of iron deficiency.

The absorption of food iron in the heme form is unique in many respects. Ascorbate and phytates, respectively, neither enhance nor impair heme iron absorption,[8, 48] nor do many foods accompanying the ingestion of heme appreciably influence its absorption. The precise mechanism whereby heme iron is absorbed is not understood. It appears that the heme molecule enters the gut epithelial cell intact, and that the iron is then released from the porphyrin moiety and delivered to the plasma transport protein, transferrin. The differences in absorption percentages between non-heme and heme iron may extend beyond the chemical properties of heme itself, since, as shown by Turnbull et al.,[48] an almost two-fold increase in iron absorbed by normal subjects occurs when heme is ingested as hemoglobin (14 per cent), compared to when it is given alone (7.8 per cent). Enhanced heme uptake in this instance may be due to favorable interactions with the polypeptide or amino acid residues present following globin digestion, as has been shown to occur with inorganic iron.[29]

Dietary Requirements of Iron

Daily iron requirements in the human vary greatly depending on age as well as sex (Table 3). With respect to total body iron, the daily requirements are proportionately greatest during the first 2 years of life. During this period the growing infant must more than double his iron endowment at birth to remain repleted. The next stress placed on iron balance occurs during the pubertal growth phase, the yearly requirement for iron absorption going from levels of about 200 mg. prepubertally to a peak at age 14 to 15 of 400 to 500 mg.

Since menarche imposes the extra burden of blood loss on the female at this time, one would expect that her requirements during puberty would exceed those of the male. As pointed out by Hawkins,[21]

Table 3. *Yearly Iron Requirements of Males and Females at Different Ages*[21]

AGE (YEARS)	IRON INCREMENT* (MG/YEAR)		TOTAL IRON LOSS (MG/YEAR)		IRON ABSORPTION REQUIRED (MG/YEAR)†		DIETARY IRON REQUIREMENT§ (MG/DAY)	
	M	F	M	F	M	F	M	F
Birth–1	134	100	9	9	143	104	3– 7	2– 6
1– 2	140	145	16	16	156	161	3– 7	3– 7
7– 8	146	140	52	50	198	190	4–10	4–10
12–13	308	184	116	378‡	424	562	9–22	12–28
14–15	401	12	161	387‡	562	399	12–28	8–20
20–21	77	87	260	416‡	337	503	7–17	11–24
60–70	–118	–60	221	155	66	77	2– 4	2– 4

*Total yearly iron increment to hemoglobin, enzymes, storage, etc.
†Calculated: (iron increment plus iron loss)
‡Includes menstrual losses
§Range based on 13%[21] and 5.3%[39] mean absorption of iron from foods

boys during this period have an equally great if not greater iron requirement because their pubertal incremental needs for iron exceed those of the female. This is because boys not only undergo greater growth during puberty but also acquire a relatively greater hemoglobin mass at this time.

Toward the end of this growth period, women have a higher daily iron requirement than do men, which remains true throughout the child-bearing period. After age 60, the iron requirement for both sexes becomes about the same.

DIAGNOSIS OF IRON DEFICIENCY

The physiologic and biochemical changes occurring in iron deficiency do so in a predictable and orderly sequence and are summarized in Table 4.

Marrow Iron

The first abnormality to occur is a reduction in and the eventual disappearance of hemosiderin from the marrow and from other organs of the reticuloendothelial system. A number of excellent studies[5, 37] have established the value of examining the marrow aspirate or biopsy for hemosiderin, either directly or following Prussian blue staining, and point to this procedure as being the most sensitive and accurate means of evaluating the status of iron nutrition.

With rare exceptions, such as in anemias associated with brisk hemolysis accompanied by markedly increased iron turnover (e.g., those due to autoimmune hemolysis or the hemolysis accompanying increased flow turbulence following cardiac prosthetic surgery), all other anemias are associated with normal or increased marrow iron. The studies of Nixon and Olson[37] have extended the value of the marrow iron survey beyond just the diagnosis of iron lack, having shown that hemosiderin particle size and distribution afford valuable clues of iron turnover rates. Anemias associated with increased turnover following blood loss or hemolysis are accompanied by smaller hemosiderin marrow particles. With depressed iron turnover rates, such as occur with anemias of infection and metabolic disturbances as well as aplastic anemia, larger marrow hemosiderin particles are found.

Of the experimental studies done to establish low iron stores without performing a bone marrow tap, those of Fielding et al.[17] are of interest. These workers simultaneously injected the potent iron chelator

Table 4. *The Sequence of Changes in Iron Deficiency*

I.	Depletion of marrow iron (hemosiderin and ferritin)
II.	Elevation of serum iron-binding capacity above 350 micrograms per 100 ml.
III.	Decrease in serum iron concentration below 50 micrograms per 100 ml. and drop of transferrin saturation index (below 15 per cent)
IV.	Mild anemia (10–12 gm. per 100 ml.)
V.	Erythrocyte hypochromia and microcytosis with increasing anemia

deferoxamine and its ^{59}Fe-labeled chelate, ferrioxamine, and then determined the specific activity of the iron complex in the urine, as a measure of tissue mobilizable iron. An inverse relationship between the above was noted, which suggests that this procedure may be of use in diagnosing early iron lack in the future. One drawback to this technique is that it necessitates the use of radioactive compounds; however, in subjects averse to marrow puncture it may prove to be a workable alternative.

Serum Iron and Iron Binding Capacity

Following the disappearance of marrow iron stores, an elevation in the plasma iron-binding protein, transferrin, occurs usually to levels above 350 micrograms per 100 ml. followed by a drop in serum iron below 50 micrograms per 100 ml., giving a saturation index of less than 15 per cent (saturation index = serum iron/total iron binding capacity × 100). Although an index of less than 15 per cent is highly suggestive of iron lack, values between 10 and 15 per cent may occur in chronic infections wherein serum iron values may be severely depressed without a proportional lowering of the iron-binding capacity.[2]

Not to be overlooked are the possible errors in the routine laboratory analysis of serum iron, since the metal is present in serum in micro amounts. A normal concentration of 100 micrograms per 100 ml. is equivalent to one part in a million, and thus minimal iron contamination from reagents or glassware may markedly alter the value. An additional variable to be reckoned with is the diurnal variation that the serum iron normally undergoes.[40] Differences of from 20 to 40 micrograms per 100 ml. have been observed in normal adults between morning and evening values, the higher levels usually occurring earlier in the day.

Elevation of the plasma iron-binding protein usually accompanying iron lack is also not only subject to analytic error but varies widely in iron lack, correlating poorly with the degree of deficiency. It is also subject to spurious elevations, e.g., during pregnancy, and acute hepatitis, and following the "pill."[7] The serum iron is also elevated in this latter instance, which may further reduce the value of these parameters in the evaluation of the iron status of women receiving oral contraceptives.

Anemia and Other Clinical Findings

The next change occurring in the natural history of iron lack is the onset of a mild anemia. The characteristic red cell changes of microcytosis and hypochromia may or may not be evident during the incipient stages of deficiency. As the anemia progresses, however, these changes always occur, often to the extent where many of the red cells appear as membrane ghosts, with only a very thin outer rim of hemoglobin remaining.

Although occurring in a minority of patients with iron deficiency, glossitis, dysphagia, and spooning of the nails are clinical findings which should alert the physician to the diagnosis. They may make their appearance at any time during the development of the deficiency state.

Since the depletion of marrow iron precedes the onset of anemia in the natural history of developing iron lack, we must then consider that the non-anemic patient lacking demonstrable iron stores is incipiently deficient and deserving not only of iron therapy but also of a diagnosis as to why. Symptoms of easy fatigue, irritability, etc. (the tired housewife syndrome) may also be present during the early phase of iron deficiency, as shown by Beutler et al.,[4] and may improve with iron repletion.

THERAPY OF IRON DEFICIENCY

It is well to re-emphasize at this point that in cases of iron deficiency other than in infants and the pregnant woman, a thorough search for the cause, most probably pathologic blood loss, is mandatory and deserving of the utmost perseverence on the part of the clinician.

Choice of an Iron Preparation

Once the diagnosis of iron lack has been made, the treatment of choice is iron, in most cases iron alone administered orally. Ferrous sulfate (USP) is an excellent preparation for this purpose.[22, 44] Other iron salts such as iron fumarate, gluconate, and succinate can be prescribed but offer no advantage and may be more costly. Since most ingested medicinal inorganic iron is absorbed in the first part of the small bowel, the use of slow-release formulations, thought to be less irritating to the gastrointestinal tract, has little physiologic justification. Carefully performed absorption studies[6] have shown that these preparations are only one-fourth to one-sixth as effective as ferrous sulfate solutions in providing absorbable iron.

The prescribing of multivitamin multimineral preparations in simple iron deficiency has repeatedly been deplored, and for good reasons.[22, 50] Firstly, in iron lack, response[6, 22] to the metal is in no way hastened by the alphabet of vitamins and the generous smattering of the periodic table of elements that find their way into so-called "hematinic" preparations. Secondly, if other deficiencies are present, this shotgun approach to therapy will mask them when indeed their recognition may be of importance. The folic acid frequently included in these mixtures given to the vitamin B_{12} deficient patient may delay the correct diagnosis and treatment to the point of permanent neurologic impairment. The pinch of vitamin B_{12} (1.5 to 10 micrograms) put into these preparations for the person with pernicious anemia, the most common cause of vitamin B_{12} lack in the United States, is of no therapeutic value given orally. Lastly, although vitamin C (ascorbic acid) does enhance the absorption of some types of food iron, and small doses of inorganic iron as well, at therapeutic dose levels of iron (Table 3), this vitamin affords little if any enhancement of iron uptake.[6, 35]

The matter of cost to the patient for these concoctions must also be considered in view of the increasing sensitivity to the rising cost of health care. In 1969 the pharmaceutical industries' wholesale volume of hematinics exceeded $44 million.[11] Add to this the retail cost to the

Table 5. *Comparative Cost of Oral Iron Therapy. Ferrous Sulfate (USP) vs. "Hematinics"*

PREPARATION	ELEMENTAL IRON PER TABLET (Mg)	COST PER TABLET	MONTHLY COST OF THERAPY*
Hematinic A	40	$0.05	$ 7.50
Hematinic B	67	$0.07	$ 6.30
Hematinic C†	10	$0.07	$21.00
Hematinic D	100	$0.10	$ 6.00
USP ferrous sulfate, 0.3 gram tablet	60	$0.004	$ 0.36

*Based on a dose of 180 to 200 mg. of elemental iron daily
†Preparation grossly inadequate in iron content for treatment of deficiency state

patient of his filled prescription and the illspent money for over-the-counter iron/vitamin mixtures, and this sum becomes only the tip of the iceberg. To emphasize this point, the relative monthly costs of iron therapy using four popular trade name hematinics vs. USP ferrous sulfate are shown in Table 5. Ferrous sulfate 0.3 gm. tablets USP, can be readily purchased over the counter in "childproof" bottles for less than ½¢ per dose. At a dose of 0.3 gm. three times a day,[2] which is equivalent to 180 mg. of elemental iron daily, effective iron repletion therapy can be achieved for less than 2¢ per day. Contrast the cost to the patient of the same iron dose prescribed in a trade brand hematinic and the cost rises 10 to 20 times, and even higher, since some preparations (hematinic C, Table 5) are woefully inadequate in iron content for therapeutic purposes.

Dose and Duration of Therapy

The objective of therapy in iron deficiency is not only to provide sufficient iron for the normalization of the hemoglobin mass but also to restore iron stores to normal (20 per cent of total body iron).

In the absence of heavy bleeding, 180 to 200 mg. of elemental iron daily given orally in three divided doses in simple iron deficiency should produce a hemoglobin response of from 1 to 2 gm. per week, depending on the initial degree of anemia.[2] In adults, no appreciable hemoglobin elevation should be expected until the second week following the institution of therapy. The reticulocyte peak occurs anywhere from 7 to 12 days after starting therapy and may reach levels of 15 to 30 per cent. This level falls off rapidly, and in the presence of a continuing hemoglobin response may be only 2 to 3 per cent above a baseline level of 1 per cent. Thus unless the patient can be closely monitored on a daily basis, the hemoglobin increase is the more convenient index with which to assess response.

If after a month there is less than a 2 gm. rise in hemoglobin, or if the hemoglobin has not returned to normal after 3 months of treatment, the physician should suspect the following: (1) the patient is not taking his medication; (2) blood loss is continuing to deplete available iron for hemoglobin formation; (3) chronic infectious, metabolic, or inflamma-

tory processes are impairing response; (4) intestinal absorption of the orally administered iron is impaired; (5) a deficiency of folic acid and/or vitamin B_{12} is also present and requires further diagnostic workup and appropriate therapy.

Lastly, one should also consider the not too infrequent occurrence that the initial diagnosis of iron deficiency was in error. Thalassemia, sickle cell anemia, and other hemoglobinopathies, as well as congenital or acquired hemolytic anemias, should be considered and ruled out, ideally before instituting iron therapy, since iron in such instances is rarely of value and may be potentially harmful. Again, the value of observing the marrow for hemosiderin in establishing the deficiency state is emphasized. In the above anemias, with rare exception as pointed out earlier, hemosiderin is always present and very commonly found to be increased.

The oral iron dosage recommended by the American Medical Association on Foods and Nutrition is 180 to 200 mg. of elemental iron[7] daily, administered in three divided doses between meals for maximal absorption. At this level, about 85 per cent of patients will have good tolerance. However, if nausea, constipation, or abdominal discomfort ensues, the iron preparation should then be tried with meals or reduced to 100 mg. per day, at which level tolerance will be improved.[47] Although oral iron preparations (especially at levels above 200 mg. of elemental iron per day) may turn the stools black, contrary to a popular belief[19] such stools do not give a falsely positive guaiac test for occult blood.[36] If the guaiac test for occult blood becomes positive under these conditions it is due to the presence of heme from either the diet or gastrointestinal blood loss.

Since the goal of therapy is to also replenish iron stores, treatment with oral iron at therapeutic dose levels should be continued for 2 to 3 months after the normalization of the hemoglobin. A rough but useful rule of thumb is to continue iron therapy for a period twice that required for the normalization of the hemoglobin level.

Parenteral Iron Preparations

A word or two concerning the use of parenteral iron is appropriate. Although frequently a slightly faster hemoglobin response to parenteral iron has been noted over oral preparations,[26] this does not in itself justify the use of parenteral iron for therapy of simple iron lack. Situations that call for the use of parenteral iron compounds, such as iron dextran (Imferon), include the following: (1) the unreliable patient whom you suspect is not taking or refuses to take his oral medication (this includes the parent who, for one reason or another, does not or cannot give her infant oral iron as prescribed); (2) patients who have had bowel surgery that may either impair oral iron absorption or may be prone to develop symptoms of iron intolerance; (3) the patient in whom blood loss continues to be excessive, so that gut absorption of iron will not suffice to keep ahead of iron loss; (4) patients with serious bowel disease such as regional enteritis or ulcerative colitis, or those having malabsorption due to sprue. It is well to point out that with the use of parenteral iron

preparations the physician should always calculate the total dose given on the basis of both the hemoglobin and the storage iron deficits.

NUTRITIONAL COUNSELING AND PREVENTION OF IRON DEFICIENCY

If the deficiency was nutritionally induced rather than solely the result of pathologic blood loss, dietary counseling on the part of the physician becomes an integral part of the therapeutic and preventive program. This is especially true in young children, in whom iron deficiency is so common.[1]

As pointed out, milk is a very poor source of iron and yet often constitutes the major portion of the young, growing infant's diet. With the aim of preventing iron deficiency at this crucial period in life, the Children's Bureau of the Department of Health, Education and Welfare has recommended that: (1) for all infants, iron fortified food to provide at least 6 mg. of iron daily be introduced at 6 weeks of age and continued through age 18 months; (2) for infants at greater risk of becoming deficient (e.g., infants of lower socioeconomic families, bottle-addicted babies, or infants who during the newborn period sustained blood loss or required exchange transfusion) the level of daily iron intake be raised to 10 to 15 mg. per day and supplemented with medicinal iron preparations if required. Of the foods available for iron fortification, cereal was felt to be the most convenient, being both economical and most likely to be in the child's diet up to age 2 years.

The use of prophylactic iron during pregnancy has become a common practice, and rightly so, since the net loss of iron during pregnancy and delivery averages 680 mg. and may actually exceed 1000 mg. if blood loss during delivery is excessive. Closely spaced multiple pregnancies without prophylactic interim iron therapy further serve to tax iron balance. The average daily diet consumed by American women contains about 10 mg. of iron.[33] This amount in many instances is insufficient to maintain adequate repletion, since even in the presence of deficiency, less than a third of it will be absorbed.

Thus, the question arises, should adult foods as well as those of infants be more liberally fortified with iron? Probably they should, since our present day food refining and preparative methods have served to decrease the overall daily iron intake. The next questions are, however, more difficult ones, such as how much should the iron level in food be raised, and to which foods should the iron be added? Further complicating this problem is the very varied dietary habits of the American populace.

Until such questions can be resolved the major responsibility of preventing iron lack must then rest with the physician. Thus, the importance of an awareness on the physician's part of the high prevalence of iron lack as well as an appreciation of the many factors that predispose his patient to it cannot be overemphasized. It is only through these means that this most common and yet so readily preventable and treatable disease can be properly controlled.

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Nutrition and Mental Development

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In a world where population is increasing at an enormous rate, we find one half of that population not adequately nourished.[27] Moreover, this is the half which is multiplying most rapidly. In spite of the efforts in the past few years to deal with this dilemma, the situation is becoming worse. Each day several hundred thousand children are born, most of whom will be exposed to severe undernutrition during their most formative years. Some of these children will die. In some areas only half will survive. Malnutrition will be a major contributing cause of death in most of these children. Infectious diseases which are innocuous in well-nourished populations may be fatal in the undernourished child. Measles, for example, carries an extremely high mortality rate in developing countries. If this were the only dimension, the problem would be serious enough, but at least the survivors could be helped. During the past 20 years, however, evidence has been mounting that an infant who has survived a period of severe malnutrition may be seriously handicapped—handicapped in terms of his physical and mental development. The implications of such evidence are staggering. The vicious cycle which is set in motion is self-perpetuating and continues from generation to generation.[13] The malnourished infant growing up in poverty is unable to acquire the skills to deal with the complexities of modern society. The result is that he remains poor for the rest of his life and his children are born into the same social and economic conditions. The family does not have the resources to adequately nourish the new infant. He in turn becomes seriously malnourished and, if able to survive, is handicapped in such a way as to prevent him from extricating himself from the plight of his parents. Thus a condition of poverty is perpetuated and will be passed from one generation to the next. The genetic endowment is presumably normal, but the environment prevents achievement of the genetic potential. This analysis suggests that there already exists a pool of people who have been so handicapped, and that this pool is increasing in almost geometric proportions with the present-day population explosion.

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In this paper I should like to examine critically the evidence that has led to these serious conclusions, and to examine some practical possibilities for interrupting this cycle.

Studies from a variety of sources indicate that in both animal and human children a series of critical periods exists, as the brain develops, during which environmental stimuli may produce irreversible damage. We can arbitrarily divide these studies into those dealing with the physicochemical development of the brain and those dealing with the functional development of the brain. Studies in each of these areas can be further divided into those performed in animals and those carried out in humans.

PHYSICOCHEMICAL GROWTH OF THE BRAIN

Animal Experiments

Eighty percent of adult brain weight is reached by 1 month of age in the rat and by 2 to 2½ months of age in the pig. In all species of mammals so far studied, the brain reaches its ultimate weight long before the animal reaches its mature size. The brain almost invariably is the first organ to attain its final size. It was first demonstrated 50 years ago that undernutrition in rats shortly after weaning resulted in reduced brain weight, and that this reduction persisted even after the animal was nutritionally rehabilitated.[28] These results have not only been confirmed in both rats and pigs,[16, 17] but have been extended[41, 43] to show that even more marked and long-lasting effects could be obtained if the animals were undernourished from birth to weaning.[42] At present there is little doubt that malnutrition from birth to 21 days of life will result in a permanent reduction in brain weight. More recent studies in the rat have indicated that brain weight may be reduced even in utero by severe protein restriction in the mother, and that animals born to such mothers may never achieve normal brain size even if they are adequately nourished after birth.[11] In contrast, undernutrition after 3 weeks of age in the rat and after 5 weeks of age in the pig results in progressively smaller effects on brain weight and complete recovery of normal weight after rehabilitation. These studies have repeatedly demonstrated that the time in which malnutrition is occurring is critical in terms of the ultimate outcome. The earlier the malnutrition, the more severe is the effect and the less likely is recovery. It would appear that a critical period of brain growth exists in the rat and in the pig, during which the brain is most susceptible to the effects of malnutrition.

HISTOLOGIC CHANGES. Histologic changes have been observed in the central nervous systems of rats, pigs, and dogs raised from weaning on protein-deficient diets.[35, 36] Both neurons and glia in spinal cord and medulla degenerate. These changes persist even after intensive rehabilitation with a protein-rich diet lasting for as long as 3 months. The changes could be made more severe either by beginning the restriction at an earlier age or by extending the duration of the deficient diet. In pigs

[1]Personal communication.

it has also been demonstrated that severe undernutrition early in life will produce histologic changes in the cortex itself.[30] Neurons in gray matter are reduced in number and appear swollen. More recently, histochemical changes have been described in the brains of rats subjected to early malnutrition. The appearance of a variety of enzymes, demonstrable by special staining techniques is delayed and the ultimate quantity obtained is reduced.[55] Thus early malnutrition will produce specific histologic and histochemical changes within the cells of the central nervous system. Again, the earlier the malnutrition, the more severe is the damage and the more likely it is to persist.

Cellular Growth. Weight gain and histologic appearance give only a limited picture of organ growth. Organ growth may be quantitated in terms of increases in cell number and increases in the weight or protein content per cell. Since DNA is constant within any diploid cell in a given species,[3] the amount of DNA in any organ reflects the number of cells in that organ at any given time. The actual number of cells may be calculated by determining total organ DNA and dividing by the DNA content per cell.[22] Once the number of cells is known, the average weight per cell or protein per cell may be determined simply by dividing the total organ weight or protein by the number of cells.

Normal and retarded growth in the organs of the rat have been serially studied in this manner.[19] Three phases of growth were defined in all organs: hyperplasia, hyperplasia and hypertrophy, and hypertrophy alone. The transition from one phase into another depended on a slowing down and finally a cessation of DNA synthesis. The time this occurred varied from organ to organ, but in all cases DNA synthesis, as measured by total organ analysis and by incorporation of ^{14}C-thymidine, ceased before weight gain and net protein synthesis stopped.

In the whole brain, DNA synthesis stopped at 17 days, whereas net protein continued to increase until 99 days. Moreover, if the brain is divided into specific regions, these areas have their own individual growth patterns.[23] Cell division in the cerebellum proceeds at a rapid rate until 17 days and then abruptly stops. In contrast, the increase in cell number in the cerebral cortex proceeds more slowly but lasts until 21 days. In the brain stem there is an increase until 14 days and then a leveling off, whereas the hippocampus has a discrete increase between 14 and 17 days. This discrete rise in DNA content is probably associated with migration of cells into the hippocampus rather than with cell division within the hippocampus itself. Total protein content increases at a more rapid rate than total DNA in the cerebrum and brain stem. In the cerebellum, however, protein increases more slowly than DNA. Therefore, protein/DNA ratios rise in the brain stem and cerebrum but actually decrease with growth of the cerebellum.

Because previously cited experiments suggested that the recovery patterns of early and late malnutrition differed, the effects of malnutrition on these cellular growth patterns were investigated.[47]

Results indicated that early restriction interfered with cell division and that the animal was left with a deficit in the number of cells in all organs, even after adequate refeeding. Late malnutrition resulted in a decrease in the protein/DNA ratio (cell size), with recovery on refeeding.

In those animals malnourished from 21 to 42 days, all organs were reduced in weight and protein, but the brain and lung had normal DNA content, while the others had reduced DNA content. Thus, in the brain and lung, "cell size" was reduced with no effect on cell number, whereas in the other organs, cell number was reduced, "cell size" remaining normal. Only the brain and lung recovered on refeeding.

These data supported the hypothesis that interference with cell division resulted in "permanent" effects and focused attention on the first 21 days of life, at least as far as the brain was concerned. Moreover, since only the whole brain had been examined, the various regions of the brain in animals exposed to neonatal malnutrition were studied.

In rats malnourished from birth the cerebellum showed a reduced DNA content by 6 days of age, whereas changes did not appear in the cerebral cortex until 14 days. Migration into hippocampus, which usually occurs between 14 and 17 days, was delayed.[21] Thus, at least in the brain, different regions show selective sensitivity to malnutrition which appears to depend on the cellular events occurring in that region at that time. Recent studies employing radioautography have elucidated the cell types involved. Results indicate that it is not the cell type, but whether it is dividing, that is critical. Thus, postnatal undernutrition will affect only glia in rat cortex since only glia are dividing. However, in cerebellum and under the ventricles where neuronal elements are dividing, these cells are affected and their rate of cell division is curtailed.

Conversely, "overnutrition," produced by reducing the litter size to three animals nursing from a single mother, resulted in an increased brain weight which was associated with an increase in the number of cells.[48] Thus, the rate of cell division and the final number of cells could be altered in either direction by the state of nutrition. It therefore seemed possible that recovery actually might occur even if cell division had been interfered with, if the animals were refed increased quantities and if refeeding were begun before the normal period of cell division had stopped.

Animals were reared in groups of 18 until 9 days of age and then reared in groups of three until weaning. The reduction in cell number which was present at 9 days in all organs disappeared by weaning. In the brain, only the cerebellum showed a significant reduction in DNA content at 9 days, and by 21 days this reduction had disappeared.[52] These data demonstrated that during the period of hyperplasia, the rate of cell division may be increased sufficiently, by increasing caloric intake, to correct a previous deficit in cell number imposed by malnutrition. Thus, not only are the extent and duration of undernutrition and rehabilitation important, but the age of the animal at the time rehabilitation begins is also critical. It is important to note that this recovery is for total brain cell number and says nothing about individual brain regions and specific cell types.

Recent evidence of Zamenhof and associates[51] demonstrates that malnutrition during pregnancy in rats will result in offspring whose brains contain a reduced number of cells. Data from our laboratory[46] have indicated not only that this is true, but that as early as 16 days of fetal life, cell division is retarded in all areas studied and every cell

type is involved. Moreover, even if the young feed normally after birth, they do not recover and are left with a permanent deficit in brain cell number. However, it is perhaps even more significant that the effects of postnatal malnutrition on animals previously malnourished in utero are much more marked than the effects of either type of malnutrition alone. These "doubly deprived" animals are severely retarded in their growth, and their brains contain only 40 per cent of the expected number of cells. It is as though prenatal malnutrition has conditioned these animals and made them hypersensitive to postnatal undernutrition.

All these studies demonstrate that a critical period of brain growth can be defined in terms of cell division. Cell division stops in the brain long before growth per se is over. Moreover, different regions reach their final number of cells at different times. Malnutrition curtails cell division during this critical period and can permanently reduce the ultimate number of cells. In the rat this critical period of cellular proliferation lasts only until weaning (21 days of age).

Myelination. Myelin is a complex lipid made up of a number of components. About 70 percent of total rat brain cholesterol is present in myelin. Nearly all of the cerebroside and most of the phosphatidal ethanolamine (plasminogen) in the rat brain appear to be located in myelin, and about 70 percent of total brain sulfatides and sphingomyelin is also present in this complex lipid.[11] Thus, analysis for these substances will give a quantitative estimation of the amount of myelin present in the brain. Moreover, since there is very little myelin turnover within the brain, serial estimation of these components can be used to establish the rate of myelin formation. The rate of myelin formation can also be established in experimental animals by measuring the rate of incorporation of radioactive components into the myelin structure.

Myelination occurs at different times in various areas of the nervous system, and its time of onset varies in different species. The process is preceded by a proliferation of oligodendrocytes.[2] Thus, myelination is dependent at least in part on cellular growth of various brain areas, and may be influenced indirectly by factors affecting the cellular growth pattern of brain as described in the previous section.

The apparent metabolic stability of myelin constituents, once laid down, makes possible the use of analytic procedures to measure brain growth. Although certain stimuli may retard the rate of myelin formation, it is unlikely that these stimuli can actually reduce the amount of metabolically stable material already there. In this respect, myelin resembles DNA. Hence, as with ultimate cell number, total myelin content should be severely reduced only if undernutrition is imposed during that period when myelin is most rapidly being laid down. In the rat, the most rapid phase of myelination is from 10 to 21 days. The incorporation of sulfate and galactose into cerebrosides and the entry of preformed cholesterol and of cholesterol precursors into brain in vivo are maximal during this period. The same is true of in vitro incorporation of phosphatide precursors into myelin phospholipids.[11] Again, a critical period can be described, this time in terms of most rapid rate of myelination, and again, this period occurs before weaning in the rat. Malnutrition during this critical 3 week period produces substantial deficits in total

brain cholesterol and a lowering of cholesterol concentration.[17] In pigs malnourished during the first year of life, total brain cholesterol and phospholipid content are markedly reduced and cholesterol concentration is slightly reduced.[15] These changes, both in rats and in pigs, persist even when the animals are rehabilitated for a long time.

Chase and associates[8] have recently demonstrated that incorporation of sulfatide into myelin of rat brain is markedly reduced both in vivo and in vitro by malnutrition during the first 3 weeks of life. Moreover, the activity of one of the enzymes involved in this incorporation is reduced by this form of neonatal malnutrition. Again recovery did not occur with rehabilitation of the animals.

The bulk of evidence seems to establish that myelination within the rat brain occurs most rapidly during a discrete period. This period is quite similar in time to the period of cellular proliferation described in the previous section. Malnutrition at this time reduces the rate at which myelin is laid down and the ultimate myelin content of the brain. Whether this is a direct effect on the metabolic events within the cells responsible for myelin synthesis or simply a reduction in the number of myelin-synthesizing cells is unknown. The enzymatic data of Chase and associates[8] would suggest that, at least in part, the former is true. Studies of the effect of malnutrition during this critical period on regional myelination patterns indicate that inhibition of myelin synthesis occurs in cerebrum, cerebellum, and brain stem, and that this reduction is proportional to the reduction in cell number described in the previous section.

OTHER. Other chemical parameters of brain growth and maturation have not been extensively studied during experimental neonatal malnutrition. However, some evidence does exist that several other processes may be disturbed. Sereni and associates[38] demonstrated that norepinephrine and serotonin levels in the rat brain are reduced after 8 days of poor nutrition beginning at birth. However, the concentration of these amines returns to normal even if the malnutrition is continued. Studies have shown an increase in the RNA/DNA ratio in the brain after a short period of malnutrition beginning at birth. This change also disappears if the undernutrition is continued.[32] Thus, transient chemical changes, which disappear later, occur during early nutritional deprivation. The significance of these changes is still not clear. Experiments in other organs demonstrate that malnutrition will reduce the rate of protein synthesis and result in disaggregation of polysome patterns.

Current evidence also suggests that the pathways of glucose metabolism in the rat brain may change as a consequence of early malnutrition. The per cent of glucose metabolized through the hexosmonophosphate shunt increases until about 8 days of age, levels off, and then drops after weaning. Malnutrition may alter this sequence. Experiments now in progress indicate that there is a change in the activity of the enzyme DNA polymerase which is in direct relation to the rate of cell division.[4] Activity of this enzyme may provide an ad hoc index of the rate of cell division. The effects of malnutrition on the activity of this enzyme are currently being investigated.

All these studies demonstrate that the preweaning period in the rat is a time of enormous chemical change within the brain, and a time when the brain is most sensitive to the detrimental effects of undernutrition.

Human Studies

The physical and chemical changes that occur during maturation of the brain have been studied less in the human than in other species. Brain weight increases rapidly prenatally and for the first 2 years of life, and more slowly thereafter, reaching adult weight by adolescence.[11] During fetal life the brain not only increases linearly in weight but undergoes a series of biochemical changes.[21] Glycolysis is present during the second month of fetal life, oxidative mechanisms appear during the third month, and activity and localization of a number of enzymes have reached a mature pattern during the seventh month of fetal life. In addition there is evidence that the presence of acetylcholinestrase indicates tissue excitability.[32] The activity of this enzyme is localized in neurons of the anterior horn of the spinal cord as early as the tenth week of embryonic life.[18] This correlates well with the time that movement of the lower limb can be elicited by proper stimulation.[1] Two specific cell types, the Cajal-Retzius cells[20] and the monamine oxidase cells,[19] are present only in fetal life, disappearing before birth. Their function is unknown. Definite lamination of the cerebral cortex is first seen around the twenty-seventh week. These data suggest that a number of critical periods may occur during development of fetal human brain. The effects of adverse stimuli on this development have not yet been studied. Investigations of brains from thirty-one normal children, who died of accidents, poisonings, or crib deaths, and from fetuses removed at therapeutic abortions, indicate that the number of cells within the brain increases linearly until birth and then more slowly until about 8 months of age, after which there is little if any increase in brain cell number.[15] Histologic studies of the cerebral cortex suggest that most neuronal division has ended by the time of birth. However, whether neurons in other areas divide postnatally is unknown. The most rapid period of myelin synthesis in the human brain appears to be around birth, but significant synthesis is still occurring at 2 years of age.[21]

Brown[5] has shown that malnutrition during early childhood will reduce brain weight. There was a marked decrease in the total number of cells within the brain in ten children who died of infantile marasmus during the first year of life in Santiago, Chile.[30] Data from this study indicate that very little cell division took place from the time these children were exposed to severe malnutrition. In four of the cases the DNA content was about 40 per cent of normal. These four children all weighed less than 2000 grams at birth. Unfortunately, their gestational age was not known. These data, however, suggest either that low birth weight infants are more susceptible to neonatal malnutrition or that significant malnutrition has occurred in utero. Studies of lipid content in human brain after severe early malnutrition confirm previous findings in animals. Total lipid content as well as total phospholipids and cholesterol are

reduced. During the first 8 months of life the reduction in lipid is proportional to the reduction in DNA and hence the lipid/DNA ratio or lipid per cell is normal. However, if the malnutrition persists beyond 8 months of age, then the lipid/DNA ratio falls, indicating less lipid per cell.[37]

Regional studies indicate that postnatal cell division is more rapid in cerebrum than in cerebellum, and stops at about 8 to 12 months in both areas. In brain stem, cell division occurs at a slow rate throughout the first year of life. Early malnutrition will reduce the rate of cell division in all three of these areas, producing the most marked reduction in cerebral cell number.[53]

One type of indirect measurement of brain growth is unique to human studies: serial measurement of head circumference. Several groups of investigators in different areas of the world have shown that malnutrition, especially during the first year of life, will curtail the normal rate of increase in head circumference.[40] Furthermore, recent studies suggest that during the first months of life, reduced head circumference in malnourished children accurately reflects the reduced number of cells and reduced lipid content present in their brains.[51]

Hence, available evidence from human studies reinforces the data derived from animal experiments and suggests that there is a critical period of brain growth during early infancy when the brain is extremely vulnerable to the effects of malnutrition.

The effects of malnutrition on the physical and chemical growth of the brain are summarized in Table 1. Both in animals and in humans, brain growth may be retarded by malnutrition. The earlier the nutritional deprivation, the more severe the retardation. There appears to be a critical period during which cell division is rapidly occurring and myelination is proceeding at its more rapid rate. Proper nutrition is essential for these processes to proceed normally. Interruption of cell division or myelin deposition or both during this period will result in permanent

Table 1. *Physical and Chemical Changes in the Developing Brains of Malnourished Subjects*

PHYSICAL OR CHEMICAL MEASUREMENT	ANIMALS	HUMANS
Weight	Decreased	Decreased
Histology	Degeneration of neurons and glia	–
Histochemistry	Delayed enzyme appearance	–
Cell number	Decreased in total brain. Earliest effect on cerebellum	Decreased in total brain, cerebrum, cerebellum, and brain stem
Net protein synthesis	Decreased	Decreased
Cell migration	Delayed in hippocampus	–
Myelin synthesis	Decreased	Decreased
Norepinephrine and serotonin concentration	Transiently decreased	–
RNA content per cell	Transiently increased	–
Glucose metabolism	Altered	–
Head circumference	–	Decreased

deficits within the brain. If animal and human data are examined together, there is a suggestion that prenatal malnutrition may make the brain more vulnerable to a subsequent postnatal insult.

A number of questions remain unsolved. What is the functional significance of these physical and chemical changes? What is the mechanism by which they occur? Although these data construct a picture which clearly demonstrates that nutritional deprivation affects brain growth and structure, and although it is quite tempting to relate these effects to brain function, no causal relationship has been demonstrated. The physical and chemical studies at best provide only strong circumstantial evidence that functional brain damage may result from early malnutrition.

STUDIES OF BRAIN FUNCTION

Animal Experiments

When Platt and associates placed weanling rats and pigs[36] and dogs[35] born of well-nourished mothers on deficient diets, the animals showed functional signs of central nervous system damage. After only 4 days on the restricted diets, the rats developed spasmodic trembling of the head and forepaws. The pigs began to walk on tiptoe with a "hobble skirt" gait and some incoordination of the hind legs. The puppies became hyperirritable. Electroencephalographic changes could be demonstrated in all the animals. Data presented more recently demonstrate actual convulsions and periods of loss of consciousness secondary to undernutrition in puppies.[39] The clinical condition of these animals improves after a short period of rehabilitation. Thus, clinically discernible neurologic damage can be demonstrated in animals undernourished early in life. Although these changes are reversible, more subtle changes conceivably could remain.

Barnes and co-workers have confirmed these observations and in addition have observed decreased learning ability in pigs malnourished early in life, which has persisted even after long-term rehabilitation. These animals do not respond well in certain types of conditioning experiments and have difficulty in solving maze problems. Barnes and Frankova have recently shown that rats malnourished during the preweaning period demonstrate a decrease in exploratory behavior. Novakova and associates[34] demonstrated in rats that early weaning followed by inadequate diet caused a decreased behavioral response to an electric bell sound. Pigs exposed to a relatively short period of undernutrition early in life show persistent functional deficits even if they are "totally" rehabilitated. There is a mild deficit in their ability to be conditioned to a shock stimulus and a marked deficit in their ability to extinguish the conditioned response once it has been learned. Rats whose mothers were malnourished during pregnancy will show decreased exploratory behavior by 10 days of age even if adequately nourished after birth.[9] Recently, Frankova has reported that rats supernourished for the first 21 days of life also showed subsequent learning

deficits.[25] Thus both undernutrition and overnutrition in preweaning rats will result in persistent functional alterations of the brain.

All these studies are highly suggestive. Functional changes can be demonstrated, some transient and some permanent. The stimulus inducing these functional changes can be isolated in animals and proved to be altered nutrition. However, the meaning of these functional differences in terms of over-all learning capabilities is difficult to assess in animal experiments. Although inferences may be drawn about the effects of human malnutrition, the evidence is still only circumstantial. There is a need for more work employing specific behavioral testing and correlating behavioral abnormalities with biochemical data in the same animals. To this end, it should be pointed out that the neurologic symptoms described suggest cerebellar involvement, and the cellular changes produced by malnutrition appear earlier and are most marked in the cerebellum. Preliminary experiments demonstrate decreased cell number, restricted to the cerebellum, in animals having decreased exploratory behavior when tested a few days previously.

Human Studies

Neurologic abnormalities, such as apathy and lethargy, are prominent symptoms of severe malnutrition in children. Both specific and nonspecific electroencephalographic changes also may occur. However, all of these changes are variable and usually disappear with rehabilitation. Gross neurologic sequelae are rare. However, subtle neurologic changes have not been systematically looked for. It would seem to me that this should be a fruitful area for future clinical investigations.

The behavior of children who were severely malnourished as infants has been studied both retrospectively[6, 7, 26, 27] and prospectively.[11, 13, 29] It is difficult, however, in both these types of studies to isolate malnutrition as the cause of the mental deficiencies found. These children invariably come from poorer backgrounds, lower socioeconomic conditions, and a generally more deprived atmosphere than even the most carefully matched control groups. Both types of studies also suffer from the lack of standardization of intellectual tests. Tests developed in advanced countries may have little meaning in developing countries, especially if large cultural differences exist. In addition, retrospective studies, although able to examine more children, suffer from not being able to be sure of the criteria used to establish the diagnosis of malnutrition. However, even with all these problems, both types of studies provide valuable data, especially if these data are not overinterpreted and especially when they are considered in the light of animal experiments and physical and chemical studies.

In a retrospective analysis, Cabak and Najdanvic[6] demonstrated that Serbian children with a history of marasmus had significantly lower intelligence quotients than Serbian children in general. This study made no real attempt to control other environmental factors but used controls of the same racial or genetic stock. One important aspect of this particular study is that it deals with malnutrition during the first year of life. Precise time distinctions are often not made in other studies inves-

tigating malnutrition in childhood. It is interesting that this study demonstrates one of the largest intelligence quotient deficits of any of the many investigations and that the patients studied were the youngest when nutritionally deprived. The major weakness in this investigation is the lack of an adequate control group. Normal Serbian children have a certain potential not reached by the study population, but the cause of the retardation cannot be ascribed specifically to malnutrition. The control children not only were better nourished but came from much better socioeconomic environments.

Other retrospective studies in developing countries throughout the world in which more careful control groups were chosen suggested again that early malnutrition interfered with subsequent learning ability. More recently Chase[7] has reported that infants in our own country who were severely malnourished early in life performed consistently poorly when subsequently tested at a later age.

A number of prospective studies have been done or are currently being done. Stoch and Smythe,[10] studying South African children, have shown that those malnourished early in life are smaller than a control population and have reduced head circumferences and intelligence quotients even after longterm follow-up. The intelligence quotient testing has been adapted for South African children and would appear valid. However, again, the control population leaves much to be desired. The malnourished children lived in inadequate housing with no sanitary facilities, came from broken, poverty-stricken homes, and were almost entirely neglected. Control families lived in neat brick houses which had sanitary facilities; all the fathers and mothers were employed, and all the children attended nursery school. Again, we see retardation but cannot isolate nutrition as the cause. However, the study dramatically points out the long-term effects produced by this complex of social ills, of which malnutrition is certainly a prominent member.

This problem of control populations is not easily solved by using control groups from "matched socioeconomic backgrounds." Garrow and Pike[26] have attempted to employ as a control group siblings not having a history of hospitalization for malnutrition. Their data indicate that the malnourished group does catch up to the control group. Here we see the opposite problem. Under these conditions, the control children probably were also malnourished, certainly subclinically and perhaps even clinically. Thus the authors may be comparing malnourished children with malnourished control children. It is significant that both groups of these Jamaican children had poorer growth than generally accepted Jamaican norms and significantly retarded growth by United States standards. The problem becomes exceedingly difficult since one must study similar populations in which nutrition is the only variable.

One of the best series of studies to date is that of Cravioto and others[11-13] in Mexico and Guatemala. They have studied populations of uniform socioeconomic backgrounds. In these investigations, performance on psychological tests was found to be related to dietary practice and not to differences in personal hygiene, housing, cash income, crop income, proportion of income spent on food, parental education, or other

social or economic indicators. Moreover, these investigators found that the performance of both pre-school and school children on the Terman-Merrill, Gesell, and Goodenough draw-a-man tests was positively correlated with body weights and heights. These tests had been previously adapted for the Mexican population being studied. Further investigations in collaboration with the Institute of Nutrition of Central America and Panama (INCAP) in Guatemala again showed a positive correlation between size and performance. The tests included placing blocks in openings, tracing block shapes, and differentiating block shapes by feel alone. These tests were considered to be measures of visual, haptic, and kinesthetic sensory integration, respectively. This study has been interpreted to demonstrate perceptual defects in children exposed to severe early malnutrition. Again, great care was taken in these studies to standardize testing procedures and to eliminate variables other than malnutrition. Although not completely successful, these studies are of the general type that should supply more precise data.

It is significant that in these studies the earlier the malnutrition, the more profound the psychological retardation. The most severe retardation occurred in children admitted to the hospital under 6 months of age and did not improve on serial testing even after 220 days of treatment. Children admitted later with the same socioeconomic background and the same severe malnutrition but a different time of onset did recover with prolonged rehabilitation. This recovery of older children, even when severely malnourished, has been observed before. Kugelmass and associates[29] demonstrated retardation in a group of malnourished New York children over 2 years of age. With prolonged rehabilitation these children significantly increased their intelligence quotient scores. Thus, it is possible that time rather than nutritional state may be of paramount importance in determining whether or not sequelae will be permanent. Data from a study[31] still not complete indicate that Chilean children admitted to a special nutrition unit with severe marasmus below 6 months of age remain retarded in physical, motor, and mental development at least until 5 years of age (when the last testing was done). It is interesting that these survivors of marasmus are from the same population and were admitted to the same unit as those who succumbed and showed the marked physicochemical changes described in the last section. Thus, if the child died he showed reduced brain cell number and myelin content. If he survived he was permanently stunted in size and retarded in development. This is the first study, with all its obvious drawbacks, which attempts to correlate changes in brain structure with those of brain function.

A final study should be mentioned,[10] though it is still in progress and therefore cannot be critically evaluated. This is the study currently being conducted at INCAP. Aware of the inherent problems of control populations and of validity of testing, these investigators have set up a study in three villages. Great pains have been taken to assure that these villages have comparable populations. Food is supplied in one village, which is otherwise left alone; both food and social improvement are introduced into the second village; the third village is simply observed.

Table 2. *Functional Changes in the Developing Brains of Malnourished Subjects*

FUNCTIONAL CHANGES	ANIMALS	HUMANS
Neurologic symptoms	Transient; tremors, hobble skirt gait, convulsions	Transient; apathy, lethargy, or hyperirritability
EEG changes	Increased slow wave activity (transient)	
Behavioral	Decreased "exploratory" behavior	Exaggerated response to certain stimuli
	Poor ability to extinguish a response	Poor ability to extinguish a response
Intellectual	Difficulty in maze learning	Decrease in cognitive and perceptual development*

*Malnutrition has not been entirely isolated as the sole cause of these changes.

The study has gone on for only a short time, but available data suggest that supplying food alone may significantly alter subsequent mental performance.

Although all these human studies clearly demonstrate retardation in development, they only implicate malnutrition as a cause. Although more work must be done, the data are nevertheless becoming more and more impressive when viewed as a whole. Each study has its own particular flaw, but since the flaws in each study are not the same, many of the variables cancel when the studies are combined. One common denominator seems to remain: severe early malnutrition.

Even if malnutrition is not the sole cause of the retarded development which has been described, the young infant is certainly most at risk. We can certainly conclude that the complex of social ills encompassing severe malnutrition, which is prevalent throughout the world, affects the learning ability of infants. The infant population is not being protected adequately from what would appear to be permanent disability. Table 2 summarizes the functional abnormalities produced by malnutrition both in young animals and in children.

COMMENT

Three questions must be answered in assessing the consequences of nutritional deprivation on ultimate potential. (1) Does malnutrition in itself produce significant brain changes? (2) If so, are these changes functionally important? (3) Is there a time during development when the brain is most susceptible to these changes?

The animal evidence presented seems certainly to establish that malnutrition as an isolated variable will produce physical, chemical, and functional changes in the brain. The data also establish that these changes are most marked and least reversible during the preweaning period in rats and shortly after birth in pigs. The meaning of these changes is difficult to interpret in animals. Certainly function is impaired, but whether these animals are retarded is impossible to say. The

weakest link in the chain of animal experiments is the lack of standardization of the behavioral tests employed and the lack of correlation between structural and chemical changes and behavioral abnormalities.

The human data again demonstrate physical and chemical changes in the brain, and the studies of nucleic acid, protein, and lipid content isolate malnutrition as the offending agent. Both these studies and the behavioral studies point to the first 6 months of life as the critical period. Furthermore, the psychological data clearly demonstrate that functionally significant retardation occurs.

The human data are weakest in answering the first question. Existing conditions within developing countries and within certain segments of our own country make it impossible to isolate malnutrition from other consequences of poverty. Certainly the complex of socioeconomic evils that includes malnutrition tends to produce retarded development. Experiments that have attempted to isolate the nutritional component have only partially succeeded. Some experiments have eliminated certain variables, while others have eliminated some of the other variables. In all, malnutrition was certainly most prominent. More data must be collected, but the evidence is becoming more and more weighty that malnutrition in infancy permanently affects the minds of the children who have been afflicted. The details have still to be worked out. How much undernutrition? What kind? When, if ever, is the brain no longer susceptible? How severe is the retardation? In other words, the degree is still an open question, but certainly severe malnutrition of young infants will produce significant brain damage.

From a practical standpoint, these conclusions are not aimed at pointing out what everyone is already agreed on—that malnutrition is undesirable. Certainly none of these experiments with animals or complicated human studies is necessary to make this point. But these studies do point out two considerations that have important practical consequences. First, as pointed out in the introduction, malnutrition is a self-perpetuating problem, a vicious cycle which begins in infancy and condemns a person to a lifetime of perhaps marginal function, making it that much more difficult for him to extricate himself from the existing conditions and to create for his family an environment which will protect his children from the same "disease." Changes in other organs produced by malnutrition are in certain situations extremely severe. They may kill the patient or keep him in a poor state of physical health, but they do not affect his ability to change his own or his family's life to the same degree as the changes produced in the brain.

Second, the time element is critical; it is perhaps the most important single finding in all these studies. Both the animal and the human data demonstrate very definitely that the earlier the malnutrition, the more severe and the more permanent are the effects. Indeed, the data strongly suggest that permanent effects will not occur if malnutrition begins after a certain age. Although the exact timing has yet to be worked out, it would appear that after infancy the brain is much more resistant to the effects of malnutrition. It is also possible that the infant whose mother was malnourished is more at risk than the infant born to a well-

nourished mother. Therefore, it would seem that the first priority should be the elimination of malnutrition in infancy and perhaps even prenatally.

In many developing countries and even in our own country, infancy has not been the prime nutritional target. A rich country such as this one should not have to establish priorities. However, at the recent White House Conference on Nutrition and Health it was again pointed out that the young infant and the pregnant woman are in an extremely vulnerable group, that a large number of people in this vulnerable group are now living in extreme poverty and are unable to provide themselves or their infants with an adequate diet. In view of the kinds of data reviewed here, certainly a reordering of our priorities would seem in order. In a poorer country strict priorities may be necessary. Although it is important to develop local protein sources, major efforts should perhaps be directed toward making prepared milk or milk substitutes with adequate protein, mineral, and vitamin content for infant feeding, with secondary considerations to similar enrichment for bread or other staple foods consumed by adults and older children.

Increasing nutrition for lactating mothers and encouraging breast-feeding are logical courses that these studies suggest. This is perhaps the most practical way at present of protecting the young infant in many countries, since breast-feeding is still widely practiced. However, industrialization often brings with it a decline in the number of women who breast-feed their children, while those who do keep it up do so for a shorter time. For example, in Chile, one of the more rapidly industrializing countries, breast-feeding is rarely practiced and the infant mortality rate during the early months of life remains among the highest in South America.[33]

As developing countries begin to emerge into twentieth century patterns, they must anticipate these changes and protect their infants. If breast-feeding is abandoned, the problem becomes much more difficult. The population at risk will increase considerably. Supplying milk alone will not solve the problem. In Chile, where free milk is available, the government has increased the supply of powdered milk to infants 12-fold during the past 10 years. The infant mortality rate has not dropped even one per cent.[33] Why is supplying milk not solving the problem? Because it is impossible, under the conditions in which she lives, for the mother to prepare a sterile formula, because no refrigeration exists, or because the milk is given to the father or sold. The net result is that the infant gets a contaminated formula, contracts diarrhea, and the mother immediately stops the formula and goes back to the tried and true and cheap method of feeding the child a gruel made from flour and water—almost total starvation.

Perhaps the ready-to-drink formulas in this country could do the most good in developing countries where breast-feeding is on the decline. Perhaps other solutions are better. Suffice it to say, the population at risk is in most cases not the population for which major nutritional programs are launched. It may be cheaper in the short run to improve the nutrition of adults and older children. But in terms of over-all cost, it

would certainly be more efficient to use the available funds to protect the population most at risk and to prevent the exceedingly costly consequences of maintaining within the society large numbers of individuals who are unable to contribute because of marginal mental development.

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Nutritional Management of Hereditary Disorders

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"We have nearly completed our knowledge of nutrition in health but we have scarcely begun to scratch the surface of the vast field of nutrition in disease."

L. E. HOLT, JR., IN HIS WINDERMERE ADDRESS, 1956.[31]

In the normal individual, a broad range of diet is consistent with good health. This is made possible by a complex series of mechanisms by which nutrients may be conserved, modified and interconverted or, if in excess, efficiently degraded and disposed of usually with the production of energy. One might have suspected that with a myriad of enzymes responsible for this complex interplay of reactions, alternate pathways could easily compensate for a deficiency in just one enzyme. Probably this can occur, but the growing list of inborn errors of metabolism has demonstrated the risk of making this assumption.

From the standpoint of the nutritionist, many of these genetic diseases have produced an organism lacking the normal versatility in handling a varied diet. The corollary is that careful control of nutritional intake, intelligently directed by the knowledge of the metabolic defect, may avoid disastrous consequences and permit normal growth and development. The purpose of the paper is to outline for the interested physician the advances in this rapidly developing field. There will be no attempt to be encyclopedic in the presentation. The volume of information is already too great, and the details of application are frequently so complex as to require the services of an expert in the setting of a medical center.

GENERAL NATURE OF THE PROBLEM

The one gene – one enzyme concept states simply that the machinery for the synthesis of a specific enzyme is under the control of a specific gene. It follows that a genetic mutation producing an inheritable disease

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is likely to produce a defect involving one enzyme. Although exceptions are being recognized in both directions—more than one gene involved in the synthesis of a single protein, and more than one protein dependent on a single gene—it remains a useful generalization for the study of genetic diseases.

The nutritional problems that flow from such enzymatic defects are dependent on the specific enzyme that is involved. A few broad categories may be described. However, not all diseases conform to this simple classification.

Accumulation of Noxious Metabolites Proximal to the Metabolic Block. The simplified diagrams (Fig. 1) demonstrate the following series of events. Under normal circumstances, nutrient A is converted to essential material X and the excesses of A are disposed of in the form of B. If the enzyme that converts A to B is defective, there is a reduction of B and an accumulation of A, which may be noxious. Phenylketonuria is the classic example.

The nutritional answer to this problem is to provide A in amounts sufficient for the synthesis of X, but avoiding the excesses that require the disposal pathway through B.

Deficiency of an Essential Material Distal to the Block. If the circumstances described above are modified so that B becomes essential to the body economy and A is non-toxic, or easily disposed of through other pathways, then nutritional correction may be achieved by the supply of B. An example requiring this approach is provided by orotic acidemia.

Inability to Conserve Essential Nutrients. The clearest example of this group is nephrogenic diabetes insipidus, in which water is not retained by the kidney. The nutritional approach is to increase the fluid intake to make up for the losses.

Vitamin Dependency. The characteristic feature of diseases in this group is the reversal of the biochemical defect by large doses of a vitamin. In some instances, the activity of the defective enzyme is enhanced directly by the addition of the vitamin, as in cystathioninuria. The most attractive explanation is that the enzyme is structurally defective and incapable of binding efficiently with the vitamin which is its cofactor. Excesses of vitamin overcome the defect. In other diseases, the mechanism of action remains completely speculative.

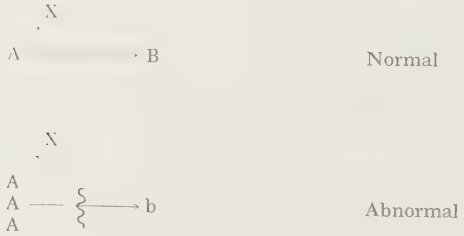

Figure 1.

Table 1. *Inherited Diseases Susceptible to Dietary Control*

Accumulation of noxious metabolites proximal to metabolic block	
Phenylketonuria	Galactosemia
Maple syrup urine disease	Ornithemia
Refsum's disease	Fructosemia
Disorders of urea cycle	Methylmalonic acidemia
Hyperammonemia	Histidinemia
Citrullinemia	Prolinemia
Arginosuccinic aciduria	Tyrosinemia
	Hyperglycinemia*
Deficiency of an essential material distal to the metabolic block	
Orotic aciduria	
Glycogenosis 1	
Pernicious anemia of infancy	
Inability to conserve essential nutrients	
Nephrogenic diabetes insipidus	Renal tubular acidosis
Chloridorrhea	Hartnup's disease
Hypoalderosteronism	
Vitamin dependency	
Cystathioninuria	Xanthurenic aciduria
Homocystinuria	Pernicious anemia of infancy
Methylmalonic acidemia	Pyridoxine-responsive anemia
Pridoxine-dependent convulsive disorder	Hydroxykynureninuria
	Tryptophanuria
Vitamin D-dependent rickets	

*Since these early observations of the effect of diet on hyperglycinemia, it has been recognized that the entity includes enzyme defects in the propionate:methylmalonate pathway, some of which respond to vitamin supplements.

Diseases that may be classified in these groups are listed in Table 1. In several instances, it has not yet been demonstrated that dietary control will reverse or prevent significant symptomatology (for example, histidinemia and prolinemia); in others, symptomatic relief is partial (for example, nicotinic acid in Hartnup's disease).

DISORDERS OF AMINO ACID METABOLISM

Phenylketonuria

This is probably the most frequent and certainly the most publicized of the amino acid dyscrasias. It is inherited as an autosomal recessive trait.[37] The enzyme defect has been identified as that of phenylalanine hydroxylase (Fig. 2).[47]

CLINICAL FEATURES.[51] The infant is normal at birth, but mental retardation generally becomes evident within a period of months. The

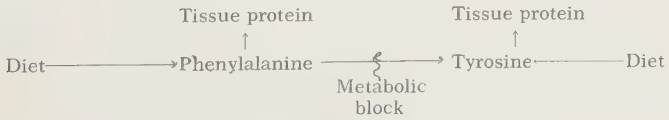

Figure 2. Phenylketonuria.

disease varies in severity, with rare patients reported to have normal intelligence. There may be associated neurological disorders such as muscular hypertonicity, tremors, convulsions, and an abnormal electroencephalogram. Eczema and a peculiar musty odor may be apparent. The patients are often blonde.

DIAGNOSIS. At present, the diagnosis is generally first suspected on the basis of routine screening tests which are mandatory in most of the United States. The bacterial inhibition test, developed by Guthrie, detects elevations of phenylalanine in the blood. It is essential that positive tests be confirmed and quantitated by the standard biochemical techniques of column chromatography or fluorescent spectrophotometry. An error in diagnosis exposes the infant to therapeutic procedures with a potential for harm, and the family to a concern that may be just as damaging. Enzyme assays are not used in diagnosis because the defective enzyme appears to be limited to the liver.[47]

TREATMENT. Phenylalanine, as an essential amino acid, cannot be synthesized or significantly stored by the human. Thus, a continuous exogenous supply is necessary. As a result, a reduction in intake will rapidly reduce the phenylalanine available to the body. As indicated in the general discussion, the metabolic defect interrupts the pathway which normally disposes of excesses of dietary phenylalanine, and the symptomatology results from the accumulation of metabolites proximal to the block.

The rational approach to treatment is to reduce the phenylalanine intake to levels just sufficient to meet the requirements for growth and tissue replacement so that the need for disposal of excesses is avoided.[3] This has been simplified by the development of a complete formula, Lofenalac (Mead-Johnson), containing fat, carbohydrate, minerals, vitamins, and amino acids with the phenylalanine concentration reduced (0.06 to 1.1 per cent). Tyrosine becomes an essential amino acid in phenylketonuria because of the metabolic block and is therefore supplied in Lofenalac. Limited supplementation of the diet with natural foods is important because there remain unrecognized nutrients that are essential for normal growth and development.

The phenylalanine requirements of a growing infant are constantly changing. To maintain the patient in balance, the plasma phenylalanine levels must be carefully monitored. An insufficiency of phenylalanine, first suggested by low plasma levels, may be as serious as an excess. If it is permitted to continue, growth is arrested and catabolism of tissue proteins occurs with the release of phenylalanine which may produce a paradoxical rise in the plasma level.

The dietary approach causes rapid disappearance of the biochemical abnormalities with the exception, of course, of the enzyme defect. There is also improvement in eczema and in general behavior. However, there is still some dispute as to whether dietary treatment permits normal intellectual development. It is true that results frequently fall short of being completely satisfactory, but most investigators are convinced that with early diagnosis and continued careful control of plasma levels, good results may be achieved. A recent report provides convincing evidence

that this is true.[33] It has been suggested that treatment may be stopped at 3 to 4 years of age when the brain is sufficiently mature.[32] The supporting evidence is not yet adequate to make a judgment.

Hyperphenylalaninemia

With the introduction of routine screening of infants for elevations of blood phenylalanine, many infants have been recognized with hyperphenylalaninemia but without the severe neurological damage observed in classical phenylketonuria.[39] Their blood levels are generally in the range of 10 to 15 mg. per 100 ml. (instead of well over 20 mg. per 100 ml.) and these tend to fall toward normal over a year or two. Differential diagnosis may be difficult early in infancy. Liver biopsy in a few of these children has revealed a reduction, rather than an absence, of phenylalanine hydroxylase.[38]

TREATMENT. Experience is too limited to be certain whether dietary treatment is necessary. Both logic and prudence would indicate maintaining the phenylalanine level below toxic levels. Unfortunately these levels have not yet been clearly defined, some investigators attempting to achieve normal levels and others accepting levels below 8 mg. per 100 ml.

THE PHENYLKETONURIC MOTHER. Phenylketonuria is not incompatible with longevity and reproduction, though both are unusual in the untreated subject. With the advent of successful dietary treatment, it may be expected that more phenylketonurics will reach adulthood. If a female phenylketonuric were to become pregnant and remain untreated, the elevations of her plasma phenylalanine would be transmitted across the placenta to the fetus and could injure the developing brain. Several such cases have been reported.[16] Dietary treatment during pregnancy is evidently indicated.

Maple Syrup Urine Disease (Branched-Chain Ketonuria)

The parallels of this disease with phenylketonuria are many. It, too, is an autosomal recessive disease in which the enzyme defect involves the degradation of essential amino acids, and the symptoms appear to be related to the accumulation of metabolites proximal to the metabolic block. However, in maple syrup urine disease three amino acids are involved and the disease is far more severe (Fig. 3). Without treatment, it

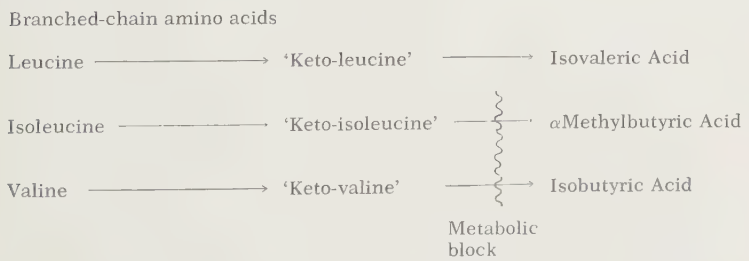

Figure 3. *Maple Syrup Urine Disease.* The branched-chain amino acids are first transaminated to their respective keto acids. The next step, oxidative-decarboxylation, is defective, involving the three keto acids.

is usually lethal within 2 weeks, and survivors are rare after 2 years. Neurological damage is invariably extensive.

CLINICAL MANIFESTATIONS. The infant is normal at birth but within a few days begins to vomit, becomes hypertonic, and often has convulsions. By the end of the first week, the maple syrup smell is generally detected in the urine.

The *diagnosis* is presumptively made by demonstrating ketoaciduria with 2,4-dinitrophenylhydrazine, and elevations in the branched-chain amino acids in urine and blood by paper or column chromatography.[11] The specific enzyme defect is demonstrable in the peripheral leukocyte.[9]

TREATMENT. The principles of dietary treatment are the same as for phenylketonuria but the application is considerably more difficult. The intake of three amino acids must be titrated, individually, so as to provide enough for growth and maintenance and yet avoid the excesses that produce rapid and severe symptoms. There is no balanced diet available, similar to Lofenalac, and so this must be done with purified amino acids.[67] During the first months of life, frequent monitoring of plasma amino acid levels is essential, because of the frequency with which the infants tip out of nutritional balance. This may be because of minor infections, changes in requirements of essential amino acids, or unknown reasons. Differentiation between excesses of dietary amino acids and an insufficiency with resultant tissue breakdown may be difficult even with the best laboratory assistance.

The consistently severe nature of maple syrup urine disease makes it simpler to appraise the value of the diet. There is no question that it is life-saving and that it will reverse the acute symptoms and biochemical derangements. If the diet is introduced early and maintained expertly, the neurological sequelae may be avoided. Natural food supplements must be introduced early to maintain growth.

VARIANTS OF MAPLE SYRUP URINE DISEASE (Intermittent branched-chain ketonuria). Genetic variants with a small amount of residual enzyme activity have a greatly modified clinical course.[10] Symptoms do not appear for months or even years after birth and are then commonly intermittent in character. In the acute episode, ataxia, lethargy, and convulsions appear in association with the maple syrup odor. In between attacks the patients commonly seem to be clinically and biochemically normal, though reductions in enzyme activity are still demonstrable. However, in one patient in our experience mental retardation persisted, probably as a consequence of repeated severe consulvions in infancy.[66]

Treatment between acute episodes may not be necessary. On occasion the total protein intake must be reduced. Purified amino acid diets have not been required. In the acute attack, parenteral fluids and electrolytes are generally effective. However, this is not always so and some attacks have been lethal.

Leucine-Sensitive Hypoglycemia

Although hypoglycemic symptoms classically occur between meals, a group of subjects have been recognized who developed hypoglycemic

convulsions shortly after meals.[6] Further investigation revealed that the hypoglycemia was induced by protein feeding, and by leucine in particular. Since then it has been realized that leucine will depress the blood sugar in most individuals, though some are particularly sensitive and are symptomatic on normal diets. However, the hypoglycemia noted on occasion in maple syrup urine disease probably reflects the extremely elevated levels of leucine and its keto acid rather than any unusual hypersensitivity.

The administration of leucine appears to increase the secretion of insulin[25] both from the normal pancreas and from pancreatic tumors. An inhibition of the hepatic output of glucose by leucine has been demonstrated in vitro,[24] possibly contributing to the hypoglycemia.

Treatment requires protein restriction with replacement with carbohydrates because most proteins contain liberal amounts of leucine. A carefully planned diet has been described.[56]

The Sulfur-Containing Amino Acids

Under normal circumstances, methionine is an essential amino acid and cystine is not. Although cystine is easily obtained in adequate amounts through diet, the human subject can also readily synthesize it from methionine (Fig. 4). The relations are similar to those that exist between phenylalanine and tyrosine, and in similar fashion an obstruction in the conversion of methionine to cystine makes the latter an essential amino acid. Two genetic defects have been described that involve the methionine to cystine pathway—homocystinuria and cystathioninuria.

Homocystinuria

An impressive series has been collected by screening patients with dislocation of the lens or presumed Marfan's syndrome, two cardinal features of homocystinuria.[58] Most of the patients were mentally retarded but many had normal intelligence. The most significant pathological finding was thrombophlebitis. Death was usually related to vascular thromboses.

A deficiency in cystathionine synthetase has been demonstrated[50] (Fig. 4). A logical approach to treatment would be the reduction of methionine intake with provision of adequate amounts of cystine. This will restore the plasma amino acid levels to normal.[52] It has been recently reported that three of four children have responded biochemically to large doses of pyridoxine.[2] However, enhancement of enzyme activity by in vitro addition of cofactor did not occur, suggesting that the mechan-

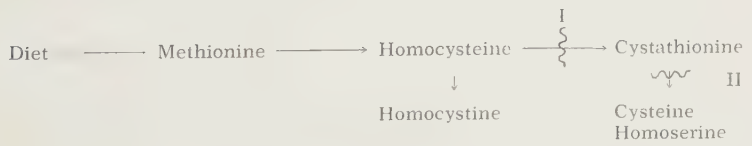

Figure 4. I, Metabolic block in homocystinuria. II, Metabolic block in cystathioninuria.

ism may differ from that of cystathioninuria[21] (see below). The nature of the disease makes long term follow-up essential before one can be certain if these approaches produce significant effects on the major features of the disease.

Cystathioninuria

Cystathioninuria was originally described in patients with mental deficiency or congenital defects. However, examination of siblings of the probands has demonstrated that the genetic defect is compatible with normal growth and development.[61] The custom of screening abnormal subjects for amino acid dyscrasias appears to have led to a spurious correlation.

The diagnosis is made by demonstration of elevated levels of cystathionine in blood and urine, and an abnormal response to a methionine load test. An increased excretion of cystathionine has been observed in unrelated diseases such as neuroblastoma, galactosemia, and hepatic malfunction.[64]

The biochemical abnormalities have been reversed in vivo with large doses of pyridoxine.[19] In vitro studies have demonstrated that, in some instances, the activity of the defective enzyme (cystathionine-cleavage enzyme) is improved by the vitamin.[18] It has been suggested that in these cases the enzyme is structurally defective. The fact that not all cases respond suggests that there are at least two different genetic defects that cause cystathioninuria.[72]

The necessity of treating responsive cases with pyridoxine is uncertain. Further observation is necessary to be confident that the condition is benign, though the experience is now strongly suggestive.

CARBOHYDRATE DISORDERS

The carbohydrate disorders fall into three groups: (1) Disorders of intermediary metabolism which present many similarities to the amino acid dyscrasias. (2) Disorders with primary manifestations in the gastrointestinal tract as the result of deficiencies in digestion or transport. (3) Storage diseases.

Galactosemia

The defective enzyme (galactose-1-phosphate uridyl transferase) is essential for the conversion of galactose into glucose.[35] As a result there is an accumulation of galactose-1-phosphate in tissues which appears to be responsible for most of the symptomatology (Fig. 5). Hypo-

Figure 5. I, Metabolic defect in galactose-kinase deficiency. II, Defect in galactosemia. The conversion to glucose 1-phosphate actually involves a series of steps, only one of which is defective in galactosemia.

glycemic attacks with convulsions may be induced by the elevations in blood galactose.

The infant appears normal at birth but feeds poorly, and vomiting and diarrhea soon complicate the picture. Jaundice provides evidence of hepatitis, which may progress to cirrhosis. Cataract formation and mental retardation is generally evident in a month or two. There is a variation in the time of onset and severity of symptoms. Death may occur in infancy.

The diagnosis is usually suspected because of the presence of a reducing substance in the urine which is demonstrated not to be glucose by chromatography or, more simply, by testing with glucose oxidase papers. Routine screening of newborn infants is now being conducted in some areas. It is important to remember that the galactosemia and galactosuria are intermittent, depending on feeding. The definitive diagnosis is made by enzyme assay of the red blood cells.[1]

Treatment consists of the elimination of lactose (a disaccharide composed of glucose and galactose) from the infant's diet. Nutramigen, in which the carbohydrate is dextrimaltose, is commonly used. As the child grows older, the problem becomes more complicated because care must be taken to avoid all prepared foods containing milk products.

Treatment rapidly relieves symptoms, and the liver pathology and cataracts may regress. However, brain damage is generally irreversible, making early diagnosis and treatment of the disease essential. With age, galactose tolerance may increase as a result of development of an alternate pathway. It would seem risky to depend on this without monitoring the levels of galactose-1-phosphate in the erythrocyte.[14]

Galactose-kinase insufficiency has also been reported. This enzyme converts galactose to galactose-1-phosphate.[22] Systemic symptoms are mild probably because there is no accumulation of galactose-1-phosphate. However, cataracts do develop.

Fructosemia

Fructosemia resembles galactosemia in many respects.[20] The first step in the metabolism of fructose is its conversion to fructose-1-phosphate. In fructosemia, fructose and fructose-1-phosphate accumulates because the enzyme defect involves the next metabolic step. The major symptoms are those of failure to thrive, hypoglycemic attacks, hepatosplenomegaly, and jaundice. However, the onset of symptoms is delayed until foods containing fructose or sucrose (a disaccharide of glucose and fructose) are introduced.

The diagnosis may be suggested by detection of a reducing sugar in the urine which is identified as fructose by chromatography. The enzyme defect is not demonstrable in the blood cells. The diagnosis is generally confirmed by the administration of fructose and determining the effect on the blood glucose.[20] In fructosemia, a prolonged fall in blood glucose is produced.

Treatment involves the removal of foods containing fructose or sucrose from the diet. Older subjects will commonly avoid offending foods as a result of experience.

Older clinicians had long suspected milk and carbohydrates as a cause of gastrointestinal disturbances, particularly in infancy. It is likely that the diagnosis was made far too frequently and was incorrectly attributed to "allergies" and "hypersensitivities." However, a scientific basis has now been demonstrated for some of these food intolerances.

Disaccharide Intolerance

The enzymatic basis is an inability to split specific disaccharides in the intestine. Biochemical interpretation is complicated by the presence of at least six disaccharidases with overlapping substrates.[7] Furthermore, more than one enzyme (for example, isomaltase and sucrase) may be missing in a patient, in apparent contradiction of the one gene–one enzyme concept. Despite these difficulties, a rational picture is emerging. Families have been reported with an intolerance for lactose, sucrose, or isomaltose and maltose. Disaccharidase deficiencies are a frequent transient complication of other intestinal disorders.

The onset of symptoms depends on the involved disaccharide. With lactose intolerance, symptoms start promptly after birth even if breast feeding is maintained. With the other disaccharides, symptoms may not appear for months until the appropriate simple sugar or starch is introduced. The major symptom is diarrhea as a result of osmotic disturbances induced by the undigested and unabsorbed sugars, and possibly contributed to by the effects of bacterial fermentation.

The diagnosis is suggested by history and confirmed by therapeutic test. There is rapid subsidence of symptoms on removal of the offending carbohydrate. Appropriate absorption tests provide more objective support of the diagnosis. For example, if lactose intolerance is suspected, an oral dose of lactose is administered and the blood glucose is determined. If the normal rise in blood glucose does not occur, transport defects must be eliminated by testing the absorption of the constituent monosaccharides glucose and galactose. A normal response with the monosaccharides would indicate that the deficiency is in the digestion of the disaccharide. Direct estimation of enzyme activity in intestinal mucosa obtained by peroral biopsy may be done but is not generally necessary.

Treatment consists of removal of the offending carbohydrate from the diet. A recent publication presenting the carbohydrate contents of various foods has simplified the devising of appropriate diets.[29]

Glucose-Galactose Malabsorption

Patients have been reported with a defect in the intestinal absorption of glucose and galactose indicating a common transport system for these two monosaccharides. The diagnosis is made clinically by obtaining flat glucose and galactose tolerance curves with normal results with fructose.[13] The defect has been confirmed in an interesting way with radioautography on biopsied intestinal mucosa.[39] An osmotic diarrhea appears shortly after birth, similar in mechanism to the diuresis induced by glycosuria.

In dietary management, glucose and galactose are replaced with fructose.

The dietary treatment of storage diseases has been generally disappointing. In the *glycogen storage diseases*, it has not been possible to reduce the glycogen deposition by controlling carbohydrate intake. However, an important cause of the symptomatology in hepatorenal glycogenosis is the inability to maintain blood glucose levels and a constant supply of this substrate to the tissues. To some extent, these symptoms may be relieved by providing frequent small glucose feedings around the clock. With this regimen, it has been possible to correct the metabolic acidosis, reduce the plasma lactate, triglyceride and cholesterol levels, restore calcium balance, and improve growth.[40] The liver also decreases in size, probably because of a reduction in fat infiltration.

Frequent small protein feedings may be helpful in controlling the hypoglycemia of debrancher deficiency.[4]

DISORDERS INVOLVING THE KIDNEY

Several genetic diseases have renal manifestations. However, in only a few of these have the urinary abnormalities been significant in the production of symptoms, and in very few has the nutritional approach proved effective. For example, renal aminoaciduria, glycosuria, and fructosuria do not cause significant loss of essential nutrients. However, nephrogenic diabetes insipidus and hyperchloremic acidosis do cause such losses, and nutritional replacement has proved effective.

Nephrogenic Diabetes Insipidus

The inheritance pattern, in its most common form, is that of an X-linked recessive.[75] Heterozygous females are generally asymptomatic, though some restriction in function is demonstrable. The disease may be also transmitted as an autosomal defect and may be manifest in the female.[8, 54]

The primary defect is lack of renal response to antidiuretic hormone. The resultant polyuria leads to dehydration with hyperosmolarity. This is particularly serious in infants who are dependent on others to provide them with adequate amounts of fluids and in whom acute dehydration may have particularly serious consequences. Failure to grow and gain weight, an irregular temperature curve with fevers, and irritability are persistent symptoms. Convulsions with other sequelae of hyperosmolarity may complicate the picture.

The diagnosis, once suspected, is easily confirmed. Despite hypertonic plasmas the urines remain relatively hypotonic and there is no response in urine volume or osmolarity to vasopressin.

TREATMENT. Symptoms subside rapidly when adequate fluid intake is provided. This may be assisted by a diet that is low in protein and salt in order to reduce the solute load to the kidneys. Occasionally, maintaining an adequate fluid intake is exhausting to the infant and interferes with maintenance of an adequate caloric intake. Under such circum-

stances, chlorothiazide may be helpful. Early diagnosis is essential to avoid serious neurological sequelae.

Renal Tubular Acidosis

The term defines a symptom complex rather than a disease. The central feature is an inability of the kidney to excrete the excess acids produced by normal metabolic processes. The urinary pH is inappropriately high, usually above 6, despite the development of a hyperchloremic acidosis. Some of the manifestations—hypokalemia, hypercalciuria, and associated nephrolithiasis—are secondary to the acidosis.

Most cases are sporadic, though familial forms have been described.[60, 74] The symptom complex may also be associated with other well-recognized syndromes such as cystinosis, vitamin D-dependent rickets, and Fanconi's syndrome. Other manifestations of renal malfunction such as phosphaturia, glycosuria and amino aciduria may be evident. The syndromes overlap in their symptoms so that sharp differentiation may not be possible. The common denominator is a defect in renal tubular function. However, the nature of the defect is variable.

Treatment is directed at the replacement of those essential materials lost through the kidney. The major loss is that of base, which is commonly replaced in the form of citric acid–sodium citrate (Shohl's solution). The correction of the acidosis may ameliorate or prevent some of the secondary manifestations such as hypocalcemia and nephrolithiasis. Phosphates have been administered when phosphaturia is a problem. The treatment and its effectiveness vary with the nature of the presenting pathology.

Familial Hypoaldosteronism

Familial hypoaldosteronism has been described[13] and can be managed successfully, though not optimally, with supplements of sodium chloride. The symptoms may be very subtle, consisting primarily of poor eating and slow weight gain. There may be a hyponatremia and hyperkalemia, but this may be transient. Elevated Porter-Silber chromogens in the urine confirm adrenal involvement, and the pattern of metabolites identifies the nature of the defect. In addition to salt administration, hormone replacement with desoxycorticosterone has been necessary to restore growth rate to normal.

LIPID DISORDERS

Familial Hyperlipoproteinemia

Several genetic disorders have been grouped under this heading.[17] Their differentiation may be difficult with current techniques and with the present state of knowledge. Some of these entities respond to a dietary restriction of fats, others to a restriction of carbohydrates. A therapeutic test may be necessary for differentiation. The differential diagnosis may be further complicated by the fact that hyperlipoproteinemia is a secondary manifestation of diseases such as glycogen storage disease, biliary obstruction, and diabetes.

Refsum's Disease (Heredopathia Atactica Polyneuritiformis)

This is an autosomal recessive disease characterized by atypical retinitis pigmentosa, hypertrophic neuropathy, cerebellar ataxia, and nerve deafness. The course is irregular with exacerbations and progressive pareses.[53]

It has been recently recognized that the enzymatic defect lies in an inability to oxidize phytanic acid, a branched-chain fatty acid, at the alpha carbon.[69] As a result phytanic acid accumulates in the tissues. The diagnosis can be made by enzyme assay of skin fibroblasts grown in tissue culture.

A unique feature of this storage disease is that the stored material is not synthesized endogenously but is derived from external sources, from foods containing either phytol or phytanic acid. Limitation of intake of plant foods containing large amounts of these substrates should prevent storage. The hypothesis has not yet been tested on an infant before phytanic acid has accumulated. To date, dietary control has been reported only in adults. There is a reduction of phytanic acid in serum and adipose tissue, and some improvement in neural conduction, sensation and muscular strength. There is no improvement in vision or hearing.[68]

It is not known whether all of the complex symptomatology results from the accumulation of phytanic acid or whether the enzyme defect has other more subtle effects. Dietary control started in infancy should resolve this issue.

MISCELLANEOUS

Hereditary Orotic Aciduria

Uridine phosphate is an essential pyrimidine that is normally synthesized in adequate amounts from endogenous precursors. In hereditary orotic aciduria the final two steps in the synthesis of this compound are interrupted (Fig. 6).[15, 65] As a result, large amounts of orotic acid are excreted in the urine.[34] However, in this instance the symptomatology appears to derive from insufficiency of the product distal to the block, uridylic acid, rather than from excesses of metabolites proximal to the block. The involvement of two enzymes controlling two sequential metabolic steps suggests a defect in the controlling mechanism of an operon, as described in the scheme for protein synthesis by Jacob and Monod.[36]

CLINICAL MANIFESTATIONS. Patients have appeared normal at birth but rapidly exhibit retardation in growth and development. The most significant clinical sign is a megaloblastic anemia that does not respond to the usual therapeutic agents. In some instances, the excretion

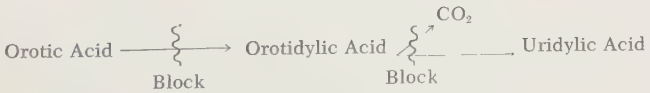

Figure 6. Orotic aciduria.

of orotic acid has been so great as to result in spontaneous formation of needle-shaped crystals, identifiable as orotic acid in the urine. A simple screening test has been devised.[55]

The response to uridine has been dramatic, with rapid reversal of the signs of anemia and resumption of growth and development.

Vitamin B_6-Dependent Convulsive Disorder

The enzyme defect has not been described, but the clinical experience suggests parallels to homocystinuria and cystathioninuria. It is a familial disease, the infants appear normal at birth but shortly begin to convulse. They respond to large doses of pyridoxine (10 mg. per day) which must be maintained to prevent symptoms.[62]

Methylmalonic Acidemia

Methylmalonic acid is an organic acid that is synthesized in the course of metabolism of a variety of precursors (Fig. 7). In turn, it enters the Krebs cycle via succinic acid. In methylmalonic acidemia, the block occurs at this step.[49]

The clinical manifestations may be complex. The most consistent is a chronic persistent acidosis, with episodes of acute exacerbation associated with vomiting and dehydration. The infants do poorly. Neutropenia and thrombocytopenia are frequent. With time, hepatomegaly, osteoporosis, and mental retardation become frequent as well.[48]

Amino acid analysis may reveal an elevation of plasma glycine. This observation led to considerable investigation before it was recognized that the fundamental metabolic defect did not directly involve glycine metabolism. An excess of organic acids can be demonstrated in the urine by simple titration, and methylmalonic acid may be identified by chromatography. The enzyme defect can be confirmed in the skin fibroblast.

The fact that methylmalonic acid is excreted in excess in vitamin B_{12} deficiency led to the evaluation of this vitamin in therapy. Some cases respond well to the administration of large amounts of B_{12} and the enzyme activity in vitro is enhanced by the addition of the active form of the vitamin.[19] The assumption, again, is that the enzyme is structurally defective in some of the genetic types of methylmalonic acidemia, and that this can be compensated for with large amounts of the cofactor.[46] A recent report describes an interesting mechanism for vitamin dependency. The defect lay in the inability to convert the vitamin into its active form.

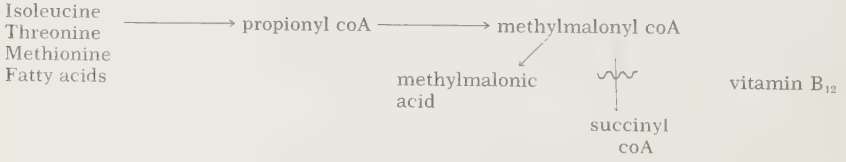

Figure 7. Methylmalonic acidemia.

Vitamin D-Dependent Rickets

Vitamin D resistant rickets has been recognized as a clinical entity for many years. The term vitamin D-dependent rickets has been assigned to some cases of this condition because accumulating information suggests parallels to other vitamin-dependent diseases.[63] It is an inherited disease with an autosomal recessive pattern. Rickets develops in spite of the usual prophylactic administration of vitamin D and in the absence of complicating disease. Phosphaturia and amino aciduria appear to be manifestations of secondary hyperparathyroidism. The symptoms can be completely reversed by large doses of vitamin D.

Although the metabolic defect and its correction by vitamin D cannot yet be explained at the enzyme level, certain possibilities have begun to emerge. It is now known that the vitamin is subjected to a series of conversions in vivo before it becomes the active form which controls the synthesis of a protein that facilitates the intestinal absorption of calcium. The intestinal absorption of calcium is impaired in vitamin dependency, and is correctable with high doses of vitamin D.[28] The reduced efficiency of vitamin D must be sought somewhere along this complex metabolic pathway.

Xanthurenic Aciduria

This has been described in mentally retarded children. The defective enzyme, kynureninase, is involved at two steps in tryptophane metabolism (Fig. 8). The diagnosis is made by identifying the tryptophane metabolites in urine. The biochemical defect may be corrected in vivo and in vitro with excesses of pyridoxine.[71] The effectiveness of this approach in preventing symptoms has not been reported.

Pernicious Anemia

Pernicious anemia appearing in infancy seems to differ from the adult form.[44] There is also an absence of intrinsic factor, but the gastric mucosa appears histologically normal and adequate amounts of hydrochloric acid are secreted. The deficiency in intrinsic factor appears to represent a specific metabolic defect leading to an inability to absorb vitamin B_{12}. Correction is by parenteral administration of the vitamin. This may be considered an example of a genetic disturbance in transport, correctable by supplying the essential material distal to the metabolic defect.

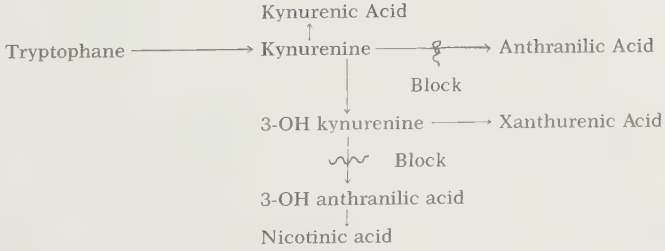

Figure 8. Xanthurenic aciduria.

CONCLUSIONS

"Inborn errors of metabolism" have contributed importantly to our understanding of the biochemistry of disease by providing clinical examples of sharply defined enzymatic defects. Similar benefits accrue from the study of the nutritional problems presented by these patients. Although the diseases are rare, the information has broad application. Similar enzymatic disturbances may be associated with more common diseases. For example, transient dissacharide intolerance commonly complicates a variety of intestinal diseases. Furthermore, our increased awareness of the variations in enzyme activities manifest among populations suggests that partial reductions in enzyme activities may be considerably more frequent than the metabolic defects recognized so far, and that these subjects may also benefit from the application of the nutritional information derived from the study of the rare inborn errors of metabolism.

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Nutrition and Cardiovascular Disease

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Clinicians, especially those without access to professional dietitians, often are made uncomfortable by questions regarding diets presented by their patients with cardiovascular disease. Hopefully, this section will offer some relief for this discomfort. Common dietary restrictions indicated for several cardiovascular conditions which can be helped through dietary alteration will be discussed.

Diet prescriptions are met with some extreme responses such as absolute defiance and fetishistic adherence. This is equally true with advice regarding smoking, activity, and drugs. Perhaps these have equal importance, but we shall limit ourselves to diet.

ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

Family History. To date, one cannot affect what has been predestined. However, if one has a strong family history of atherosclerotic cardiovascular disease or hyperlipemia, he can attempt to influence the eating and smoking habits and the degrees of activity of his progeny. The enviable low incidence of coronary artery disease among Orientals who typically eat little fat is considerably undermined by the ordinary American diet, embraced by immigrants, which contains around 700 to 800 mg. of cholesterol per day.

Smoking. No important data refute the causal relationship of the use of tobacco to all forms of cardiovascular and respiratory tract disease. The futile and dangerous use of tobacco is mentioned because of the relationship of smoking and eating. Rare is the person who defeats the habit of smoking without substitution of other orally gratifying practices.

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Thumb sucking and similar acts are not socially acceptable, so overeating and gaining weight are virtually inevitable. Gain in weight can be avoided by offering the properly motivated smoker a few relatively low-calorie substitutes for his need to "do something." During his working day he can chew sugar-free gum; munch on pickles, carrots, and celery; or suck on cinnamon sticks—all at small calorie cost. At home, he can make bouillon or eat half a portion of flavored yogurt or a few teaspoonfuls of cottage cheese—perhaps made more interesting by the addition of diced onions, pimiento, green pepper, or celery seed.

Having the patient weigh himself daily can reinforce admonitions not to overeat. Furthermore, as his endurance improves, the ex-smoker can burn more calories through exercise and the admonitions may be relaxed.

Lipid Alterations

A causal relationship has long been noted between increased levels of plasma cholesterol and atherosclerotic cardiovascular disease. Until the last few years, however, the influence of diet on plasma cholesterol had been poorly understood. Indeed, a rather large group of patients demonstrated a "paradoxical" increase in their cholesterol values while faithfully deleting animal fats and other cholesterol-rich foods from their diets, substituting sugars and other carbohydrate sources. Fredrickson clarified this problem considerably by his classification of hyperlipemia on the basis of lipoprotein electrophoresis. His division into five groups, while discrete and valid, is perhaps clinically clumsy. Type I is rare enough to ignore, type V is quite infrequent, and types III and IV can be logically grouped together on the basis of laboratory findings and responses to drug and dietary therapy.

With relative ease, the most remote practitioner can now offer his patients important dietary advice on the basis of only two readily available determinations—plasma cholesterol and triglycerides.

The patient who returns with a higher cholesterol value after adhering to a "low fat diet" probably had mixed hyperlipemia—that is, high levels of cholesterol *and* triglycerides. When a patient is deprived of meat, eggs, butter, and milk he may substitute sugars—candy, cookies, cakes, pies, and puddings—to satisfy his hunger. His body, not unlike that of the diabetic patient, cannot handle this onslaught of sugar and metabolically does the best it can in converting the load to triglycerides and, thereafter, to cholesterol. His physician, monitoring only plasma cholesterol, may falsely accuse him of abuse of his low-cholesterol diet, to which the patient has adhered religiously, although perhaps gaining weight on account of the increase in calories.

Patients having increased levels of triglycerides may conveniently be lumped together, since distinction between the Fredrickson types III and IV is virtually academic. The response is so nearly the same, it profits the practitioner little to concern himself with the niceties of palmar or eruptive xanthomata, broad-β-lipoproteinemia, and so on seen in type III hyperlipemia. Most of the patients with type IV hyperlipemia have (1) diabetes mellitus, (2) high plasma cholesterol, and (3) increased

levels of plasma triglycerides, depending on the time and circumstances of obtaining the blood sample. A moment should be spent here to point out the lability of triglyceride values, especially in types III and IV. Such patients may show severalfold increases in plasma triglycerides if the blood sample is taken within 12 hours after a meal, especially if dessert was eaten or alcohol ingested. Under such circumstances, a lipoprotein analysis also may show chylomicronemia and a marked excess of pre-β-lipoprotein.

The patient with a more marked increase in triglycerides than in cholesterol (that is, of type III or IV) can expect to have both his plasma cholesterol and (certainly) his plasma triglycerides return to normal if he exercises appropriate dietary restraint. Most if not all of such patients are above their ideal *lean* weight. This is best measured by pinching the abdominal panniculus, not by watching the scale. The latter does afford the patient a numerical goal and introduce praise or admonition to the program.

On the other hand, patients with only a high level of plasma cholesterol may not lower this value by means of harsh dietary restriction, despite carbohydrate substitution, even with weight gain. Almost by definition, patients in this group (Fredrickson type II) are relatively refractive to drug and dietary therapy, each achieving perhaps only a 15 per cent reduction in the level of plasma cholesterol.

Meals eaten the night before determinations are made have little effect in type II cases, since levels of plasma cholesterol are not so metabolically dynamic as are those of plasma triglycerides.

Dietary Therapy

We may divide the appropriate lipid diets into two simple groups depending on whether the level of plasma cholesterol alone is increased or the levels of cholesterol and triglycerides are both increased.

1. HIGH LEVELS OF CHOLESTEROL ONLY (TYPE II). This is the simpler but less effective diet. Essentially, it entails only avoiding natural sources of cholesterol. In practical terms, one can follow it by avoiding the proscribed items listed in Table 1.

The patient should eat only one or two egg yolks weekly. Total daily amounts of meat, fish, and poultry should be limited to about 9 ounces. Gravy made from meat drippings may be used after the fat has been skimmed off or (more easily) removed when hardened by chilling.

Table 1. *Summary of Dietary Advice to Patients with Elevated Cholesterol Levels*

VIRTUALLY OMITTED	AVOIDED	ALLOWED	USED FREELY
Egg yolks	Liberal use of meats	Fish	Egg whites
Animal fat	Luncheon meats	Poultry	Fresh fruits
Organ meats	Coconut oil	Cottage cheese	Fresh vegetables
Shellfish	Avocados	Sweets, in keeping with caloric allowance	Unsaturated vegetable oils
Creamy foods			

Table 2. *Summary of Lipid Defects and Response to Treatment*

FACTOR	ABNORMAL BLOOD LIPIDS	
	Elevated Cholesterol Only	Elevated Cholesterol and Triglycerides
Lipoprotein pattern	Excess β-lipoprotein	Broad β and pre-β-lipoprotein excess
Fredrickson type	II	III and IV
Dietary response	More refractory; delayed	Excellent response; prompt
Obesity	Little if any relationship	Clearly parallels lipid values
Dietary principles	Cholesterol ≤ 250 mg. daily	Weight reduction; avoid carbohydrates, calories, and cholesterol
Drugs	Nicotinic acid, d-thyroxine, and cholestyramine	Clofibrate, if dietary response is inadequate
Response to drugs	Modest	Remarkable

Coconut oil (used commonly in coffee-cream substitutes) and hydrogenated or solid vegetable shortenings are high in saturated fats; thus, they should be avoided. However, unless caloric intake must be limited, the use of soft oleomargarine and unsaturated vegetable oils may be encouraged in an attempt to achieve a better balance between polyunsaturated fats (P) and saturated fats (S), bringing the P:S ratio into the 1:2 to 1:3 range.

2. HIGH LEVELS OF CHOLESTEROL AND TRIGLYCERIDES (TYPES III AND IV). The vast majority of these patients will be either obese or diabetic. Their diet will incorporate the above cholesterol restrictions along with caloric and carbohydrate reduction; thus, in effect it is a diabetic diet with reduced cholesterol content. Such patients should be advised to avoid all foodstuffs made from or with sugar. A partial list includes syrups, jams, jellies, honey, canned fruit with syrup, pastries, ice cream, sherbet, soft drinks, and candy. Since alcohol metabolism follows a similar pathway, alcoholic beverages must be curtailed also. Fresh fruits, unsweetened canned or frozen fruits, breads, and cereals are allowed as long as caloric limits are not exceeded.

Table 2 summarizes major differences in these two situations.

CONGESTIVE HEART FAILURE

Sodium restriction is advisable in all cases of congestive heart failure. A diet containing 90 mEq. of sodium will suffice for many patients. Such a diet is usually well received, although patients with congestive heart failure often have anorexia. This, plus the effects of chronic heart failure, may lead to cardiac cachexia in long-standing cases, most commonly when there is disease of the mitral valve. It should be remembered that modest overdosage of digitalis or hepatomegaly associated with right-sided failure may contribute to anorexia. A patient with atrial fibrillation and congestive heart failure who maintains a good appetite should always be suspected of having hyperthyroidism.

Modest sodium restriction may be accomplished by avoiding pickles, olives, crackers, potato chips, pretzels, ham, bacon, salt pork, sauer-

kraut, baking soda, catsup, soy sauce, mustard, anchovies, and salted nuts. Ordinary frozen and canned vegetables may be used, with the addition of only small amounts of salt in preparation. Several salt substitutes are commercially available and are most effective when applied sparingly at the table. Since most of them are made with potassium salts, they must not be used by patients with significant renal failure.

The more strict 20 mEq. sodium diet usually is reserved for the patient with refractory congestive heart failure. It is far less palatable than diets containing more sodium and demands considerable cooperation. The above list of salty foods must be strictly avoided. Ordinary canned soups, vegetables, and meats must be avoided, and salt-free bread, butter, and cheese employed. No salt may be used in preparing fresh or frozen vegetables. If the sodium content of the water supply exceeds 20 mg. per quart, distilled water should be used.

If administration of diuretics results in hypokalemia, the following potassium-rich foods may be employed (unless limited by caloric, sodium, or cholesterol restrictions): dried fruits, especially apricots and peaches; dried beans, especially lentils; green vegetables, particularly broccoli and spinach; bananas; and citrus fruits.

HYPERTENSION

As with congestive heart failure, all patients with hypertension, regardless of etiology, should restrict sodium intake in accordance with the severity of their disease. Obesity should be prevented, or corrected if present. Potassium lost owing to the use of antihypertensive agents of the thiazide group must be replaced.

RENOVASCULAR DISEASE

As azotemia develops, proteins as well as sodium must be restricted, in keeping with the kidneys' inability to excrete nitrogenous products. If urea levels are only modestly increased, a diet supplying 90 mEq. of sodium and 70 gm. of protein may be employed. Such a diet would allow 5 oz. of meat or meat substitute (egg, cheese, fowl, or fish), 6 slices of bread, 2 cups of milk, 3 helpings of fruit, and four helpings of vegetables daily. Only slight salting at the table would be allowed.

With more severe impairment of renal function, a diet supplying only 20 mEq. of sodium and 30 gm. of protein would be prescribed. Only 3 oz. of meat or meat substitute, ½ cup of milk, ½ cup of cereal, 6 slices of low-protein bread, 2 servings of vegetables (½ cup each), 4 servings of fruit, and 11 teaspoonsful of margarine, mayonnaise, or vegetable oil are allowed per day. Depending on caloric allowance, carbohydrate supplements are supplied, including such foods as corn syrup, honey, candy, sugar, syrups, tapioca, and jellies. The potassium-rich foods mentioned previously must be avoided.

CONCLUSION

We have attempted to simplify the approach to dietary management of patients with cardiovascular disease. It is our hope that the generalizations offered will prove valuable to any practicing clinician in caring for his patients with everyday problems such as hyperlipemia, obesity, hypertension, renal impairment, and congestive heart failure.

Appended to this article is a list of references for those who wish to read deeper into the problems which have been discussed.

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Nutrition and Liver Disease

Practical Considerations

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The concept that nutrition is important in the therapy of patients with liver disease received considerable impetus from the reports of Patek and Post which attested to the benefits resulting from feeding a nutritious diet and supplements rich in the B-complex.[62, 63]

Subsequently patients with hepatic diseases, regardless of degree of severity or coexistence of complications, were managed with high protein, high carbohydrate, low fat, vitamin supplemented dietary regimens. More recent emphasis has been on evaluation of individual patients with regard to regulating protein, salt, and water intake to control hepatic encephalopathy, ascites and edema, and renal failure. This presentation outlines approaches to the management of patients with liver disease and its complications, with special reference to reconciling the need for adequate supportive nutritional therapy with the necessity for modifying intakes of nutrients. Discussion of clinical applications is preceded by consideration of the effects of liver disease on the metabolism of nutrients.†

METABOLISM OF NUTRIENTS

Abnormalities in the metabolism of protein, glucose, fat, vitamins, and minerals occur in patients with liver disease. The defects noted are not usually gross enough to induce clinical problems or seriously alter nutritional requirements in patients with uncomplicated disease. On the other hand, more overt metabolic defects are evident in patients with fulminating, progressive, or advanced chronic hepatic disease. Although

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† Although nutritional therapy is a prime consideration in the medical management of patients with liver diseases and their complications, many other aspects also must be considered in providing them with proper care and treatment.[25, 26, 33, 74, 80, 84, 85]

the significance of many of these is not established, some relate closely to serious complications of hepatic disease.

Protein

Numerous studies dealing with the metabolism of protein, amino acids, and ammonium in patients with hepatic disease have been published, especially since the relation of abnormalities in nitrogen metabolism to hepatic coma attracted widespread attention.[25, 32, 66, 71, 76] Selected studies with nutritional implications are mentioned here.

Fecal nitrogen excretion in patients with cirrhosis of the liver is normal over a wide range of dietary protein intakes.[28, 33] Absorption and postabsorptive metabolism of protein are not grossly deranged.[5, 83] Stool nitrogen is increased when non-absorbable antibiotics, such as neomycin, are used.[3, 20, 36] This may be an important consideration, especially when severe degrees of protein restriction are necessary.

Patients with cirrhosis who are given diets devoid of protein but adequate in calories excrete quantities of nitrogen in the urine comparable to those noted in normals given similar diets, indicating that "endogenous" nitrogen metabolism is not excessive.[33] Inordinately high intakes of protein are not necessary to achieve positive nitrogen balance in patients with liver disease. Most cirrhotic patients are in nitrogen equilibrium or positive balance at protein intakes of about 35 to 50 gm. per day (0.5 to 0.7 gm. per kg. per day),[33] values comparable to estimated minimal requirement for normal adults.[38] Portal systemic shunts, either occurring naturally or constructed surgically, do not seriously alter nitrogen balance.[11, 23, 33] Information on the above points was achieved by study of relatively asymptomatic patients with stable cirrhosis, some of whom had ascites. Whether or not these data apply to patients who are acutely or progressively ill or are suffering from hepatic coma cannot be stated.

Progressive decreases in urinary amino acid and nitrogen excretion occur as active liver disease subsides, suggesting less efficient utilization of dietary protein with acute liver injury.[28, 30] Aminoaciduria and altered serum amino acid patterns have also been noted in patients with cirrhosis, viral hepatitis, and alcoholic hepatitis, and coma.[16, 30, 41, 46, 60, 89, 93] Also, intermediary metabolism of certain individual amino acids (glycine, methionine, tyrosine, leucine, cystine) is not normal in cirrhotic patients.[7, 40, 41, 45, 55, 56, 90] Although these abnormalities undoubtedly point to deranged intermediary metabolism, the urinary losses of amino acids per se are usually not great enough to alter nutritional requirements.

Androgenic steroids have been used in the nutritional management of patients with acute and chronic liver diseases. Nitrogen balance studies indicate that their anabolic effect is not great. Increasing dietary protein intake achieves positive nitrogen balance more readily and more safely than administration of testosterone.[29] Giving some androgenic steroids also carries the risk of inducing liver injury. To what extent and in what way anabolic steroids influence protein tolerance in patients with encephalopathy who require dietary protein restriction is not well established. Anabolic steroids are not used in our clinic. Certainly their

use does not replace paying attention to the proper diet and insuring that the food provided is consumed.

Since emphasis recently has been on avoiding high protein intakes in patients with hepatic diseases, solutions of amino acids for intravenous use are not now commonly employed. Past studies, however, demonstrate that parenterally administered amino acids are not wasted in the urine in excess and are well utilized. Patients given amino acids parenterally as the sole source of nitrogen with adequate calories and vitamins improved clinically.[17] On the other hand, hepatic pre-coma has resulted from amino acids given intravenously in large quantities or at rapid infusion rates.[91]

Carbohydrate

The digestion and absorption of carbohydrates and glucose are normal in patients with liver disease.[8, 83] Fasting blood sugar values are almost always normal even in acutely ill or comatose patients.[81] Cirrhotics may have a diabetic type of tolerance curve after oral administration of glucose, which may be exaggerated when portal systemic shunting exists. Often the peak values are followed by exaggerated depressions of blood glucose levels. The abnormal tolerance curve is not associated with persistent glycosuria or signs and symptoms of diabetes. Treatment with insulin or oral hypoglycemic agents is not indicated; nor are high calorie feedings, or use of glucose parenterally contraindicated. However, some patients with cirrhosis and abnormal glucose tolerance have coexisting diabetes mellitus, and a few have hemochromatosis. In these cases utilization of ingested calories, and probably adequate healing of liver as well, depends upon control of the diabetes.

Episodes of symptomatic hypoglycemia may occur occasionally in patients with fulminant hepatitis,[72] fatty liver,[50] or hepatoma.[48, 75] Hypoglycemia is a prominent feature of fatty liver associated with encephalopathy in children (Reye's syndrome).[69] Usually blood sugar levels are maintained and symptoms controlled by giving glucose intravenously.

Gross defects in intermediary carbohydrate metabolism may be evident in patients with hepatic coma. Blood levels of pyruvic acid and lactic acid are elevated and increase even more after glucose is given. Elevated levels of alpha-ketoglutaric acid also occur. The levels of these keto-acids increase progressively as the patients become more comatose.[1, 2, 15, 77, 87] Although abnormalities in the Krebs citric acid cycle have been incriminated in the etiology of hepatic coma, their significance is not firmly established. Thus far no therapeutic measures are known to modify the abnormalities, but they tend to reverse if the liver disease improves.

Fat

There is no rationale for routinely recommending low fat diets for patients with liver disease.[13] Limiting fat intake detracts from the palatability of the diet and often makes achievement of adequate calorie intake difficult. Most patients with Laennec's cirrhosis, postnecrotic

cirrhosis, and acute hepatocellular diseases of various etiologies tolerate substantial levels of dietary fat (150 to 200 gm.) without adversity.[10, 35, 39, 59, 62, 63] Accordingly, dietary fat intake is not restricted unless patients complain of gastrointestinal tolerance from it. This usually occurs in patients who have deep jaundice and a decrease or absence of bile pigments from the gastrointestinal tract, as in the cholestatic phase of infectious or drug-induced hepatitis. In these cases, restricting fat intake is usually necessary only for short periods. Dietary fat is increased to tolerance as soon as urinary urobilinogen excretion increases and bile pigments appear in the stool.

Some patients with cirrhosis have fat malabsorption.[57, 86] In most cases steatorrhea is mild (e.g., about 10 gm.) compared to normal stool fat (< 5 gm. per day), and is not clinically important. Occasionally, however, patients with liver disease demonstrate steatorrhea in excess of 30 gm. daily. Possibly this is more prone to occur in patients with alcoholic cirrhosis who have coexisting pancreatic or intestinal malfunction. In these instances a trial of therapy with preparations of pancreatic enzymes given orally is worthwhile. Medium chain triglycerides orally at relatively low doses (40 to 60 gm. per day) have also been used.[57] Abdominal pains, diarrhea, and abnormal blood and cerebrospinal fluid fatty acid levels result from high doses. Some patients given medium chain triglycerides develop decreased tolerance for protein, a serious consideration in those susceptible to encephalopathy.[58] Available preparations of medium chain triglycerides also contain sodium, a disadvantage for patients with ascites and edema. These preparations are also relatively expensive. This type of therapy is not generally employed, but deserves further development and evaluation.

Steatorrhea is often of more significance in patients with biliary cirrhosis (primary or secondary), and may lead to deficiencies of calcium and of fat soluble vitamins, especially in children.[4, 42, 82] Children are predisposed to develop rickets, and adults to develop osteoporosis. Bleeding tendencies result from hypoprothrombinemia due to vitamin K deficiency. Supplements of fat-soluble vitamins are given to treat and prevent these complications.

A sprue-like syndrome is associated with the use of neomycin, a nonabsorbable antibiotic used in the treatment of hepatic encephalopathy.[3, 20, 36] The chemical pattern resembles that seen in patients with idiopathic steatorrhea. The changes in stool composition are relatively mild and probably nutritionally insignificant.

Several defects in the intermediary metabolism of fat have been described in patients with liver disease. Compared to normal subjects, patients with cirrhosis of the liver demonstrate diminished ketogenesis in response to starvation and to feeding of fat.[68] The blood ketone levels also decreased less after food ingestion in the cirrhotics than in the normals. Hepatic clearance of medium chain fatty acids is also impaired, as reflected by markedly increased serum levels after they are fed.[57, 58] The nutritional and clinical implications of these observations are not known.

Calories

Ideally, calorie intake should provide for healing and regeneration of liver, maximum sparing of protein, and general nutritional rehabilitation. Some patients recovering from acute or chronic hepatic disease eat well and, accordingly, adequacy of intake poses no problem. More often, however, patients with persisting or chronic liver disease show progressive wasting of body tissues, presumably due to inadequate calorie and protein intakes attributable to anorexia. Adequate calorie intake is not always readily achieved, especially during symptomatic episodes of illness. Presenting large amounts of food to anorectic patients is demoralizing, causes gastrointestinal symptoms, and leads to further diminution of intake. It is of more ultimate benefit to begin by offering a quantity of food that is likely to be consumed, even if the total intake is initially marginal. The first aim is to achieve an intake sufficient for maintenance and prevention of further nutritional deterioration (about 25 to 30 calories per kg. per day). The food is often accepted better if offered in frequent small feedings. Patients with liver disease usually take breakfast well and lunch fairly well. Toward evening their desire for food decreases. Advantage can be taken of this pattern of appetite in meal planning. As diet is tolerated, 200 to 300 calories daily are added at intervals of several days until intakes of 40 to 50 calories per kg. per day are achieved. The benefits, if any, from further increasing caloric intake are not established. Many patients improve with lesser calorie intakes.

The minimal caloric intake needed to achieve maximal nitrogen sparing has not been established. However, relatively stable cirrhotics who are given diets virtually devoid of nitrogen excrete minimal amounts of "endogenous" nitrogen in the urine when fed 1600 calories as glucose orally or intravenously, or as fat and carbohydrate orally.[28, 33] Although this calorie intake is sufficient to prevent utilization of body nitrogen for energy requirements, higher intakes are considered desirable.

Patients unable to eat because of vomiting, stupor, or coma are given appropriate solutions of electrolytes and glucose (10 per cent when possible) intravenously. Feeding by nasogastric tube is relatively safe, and is worth considering when intake is grossly insufficient for protracted periods. In patients intubated for upper gastrointestinal symptoms or bleeding, feeding is initiated via the tube when the clinical situation permits. Infusions of fat emulsion (900 calories) have been given to patients with cirrhosis, in addition to a diet, without apparent serious adverse effects.[43] Experience with infusions of fat emulsions is limited, and their routine use is not recommended.

Vitamins

Vitamin intake may be inadequate, especially in alcoholic patients with liver disease. Blood levels for some vitamins are elevated, and for others are decreased, in patients with acute or chronic hepatic diseases. Liver content of some water and fat soluble vitamins is reduced.[52, 53]

Giving vitamins does not always correct these abnormalities, but they tend to become normal with improving liver function. Defects in intestinal absorption and transport of thiamine have been observed in undernourished alcoholics with fatty liver.[52, 88] Alterations in the intermediary metabolism of thiamine, niacin, and folate have also been described.[12, 22, 27, 92] The illustrative observations cited demonstrate the multiplicity of factors which influence metabolism of vitamins in patients with liver diseases. The interpretation of such observations is controversial. Some authors claim that supplementary vitamins protect liver cells from injury and aid hepatic regeneration.[51, 52] Others claim that supplementing an adequate diet with vitamins does not bring about more prompt or complete recovery than might be accounted for by diet alone.[14, 24, 47]

Patients with non-alcoholic acute hepatic illnesses whose intakes are suboptimal for short periods of time are not prone to develop signs of vitamin deficiency diseases. Neither are patients with uncomplicated chronic disease, unless some incident intercedes to seriously jeopardize food intake, alter absorption, or increase demand. However, the incidence of nutritional diseases is high in patients with cirrhosis who are admitted to hospital after episodes of heavy drinking. The nutritional disorders are usually explainable by inadequate intakes. Wernicke's syndrome, peripheral neuropathy, and nutritional macrocytic anemia due to folic acid deficiency occur frequently. Beriberi, riboflavin deficiency, pellagra, and scurvy are seen less frequently. Parenteral doses of vitamins are given to correct the specific deficiencies. Since most often multiple deficiency diseases coexist, a multivitamin preparation is given parenterally, usually in intravenous infusions used to correct hydration and electrolyte abnormalities. Multivitamin tablets are given orally for a week or two, and then vitamin therapy is gradually discontinued as adequate dietary intake is achieved. Oral vitamin supplements are also provided to patients with hepatic encephalopathy whose protein intakes are severely restricted and, accordingly, their intakes of B-complex vitamins compromised. Vitamin supplements are not used routinely in the long-term management of our patients with liver disease.

The vast majority of patients with liver disease who demonstrate signs and symptoms of vitamin deficiency diseases respond promptly and adequately to appropriate specific therapy. A few patients have been described with thiamine deficiency (Wernicke's syndrome, and peripheral neuropathy) whose clinical and biochemical findings were not reversed by adequate therapy until liver function improved.[12, 22] Apparently in these cases the damaged liver was unable to metabolize the vitamin into an active form, possibly because of limited capacity to phosphorylate[92] or convert thiamine to transketolase.[22]

Patients with acute or chronic liver disease seldom require supplements of fat-soluble vitamins. Deficiency of vitamin K may occur in patients with cholestasis, or when the gut flora is altered by antibiotics. Hypoprothrombinemia may be alleviated, in part at least, by the intramuscular administration of a vitamin K derivative. Patients with significant steatorrhea secondary to biliary cirrhosis may require supplementa-

tion with fat-soluble vitamins A, D, E, and K. Vitamin K is given intramuscularly at intervals of 3 or 4 weeks to patients receiving cholestyramine for pruritus due to biliary cirrhosis. Cholestyramine is steatorrheic, and bleeding due to vitamin K deficiency is a potential complication of its use.

Minerals

The bulk of information available about mineral metabolism in patients with cirrhosis of the liver concerns the relation of sodium, potassium, and other electrolytes to fluid retention, hepatic coma, and renal failure. These aspects are discussed to some extent in this report, and extensively elsewhere.[25, 26, 74, 79, 80, 84, 85]

Iron deficiency anemia secondary to inadequate intake or blood loss or both occurs in patients with chronic liver disease and is usually treated with oral iron preparations. Iron is not given for longer than necessary, because cirrhotics are prone to develop hemosiderosis. If parenteral iron preparations are used, doses are also carefully calculated to prevent iron-overload. Hepatic dysfunction in Wilson's disease (hepatolenticular degeneration) results from excessive deposition of copper in the liver. Restricting dietary copper is an important aspect of treatment for patients afflicted with this disorder.[73]

Deficiencies and abnormalities in metabolism of other metals such as calcium, magnesium, and zinc also occur in patients with hepatic disease. Since their significance in the medical management of patients with acute and chronic hepatic disease is not established, recommendations cannot be made at the present time. For now, these are probably best provided in a well balanced, nutritious, adequate diet. The reader is referred to a recent review for further discussion of trace elements in liver disorders.[67]

CLINICAL CONSIDERATIONS

Carefully designed and controlled studies concerning the effects of diet on the course and outcome of patients with acute hepatocellular diseases are few. Most of these were done with populations of young, healthy adult men in military service during epidemics of viral hepatitis. Whether the findings can be applied to endemic hepatitis as it occurs in a civilian population and to all hepatitis epidemics is a matter of conjecture. One study of soldiers with infectious hepatitis demonstrated a slight benefit for patients who were force fed a high protein (150 gm.), 3000 calorie diet.[10] On the other hand, in another study volunteers with serum hepatitis allowed to eat ad libitum fared better than those who were force fed.[54] What influence, if any, attention to support of nutrition and to diet manipulations have on the course and ultimate outcome of patients with drug-related hepatic injury or acute alcoholic hepatitis has not been investigated, although therapy is based primarily on nutritional considerations.

Fatty liver is the dominant histologic lesion in some alcoholic pa-

tients who imbibe excessively. Although improvement subjectively and as judged by liver function may occur with diets grossly deficient in protein, return of liver fat content to normal depends upon availability of dietary protein.[18] Large amounts of protein are not needed to accomplish this favorable end. In fact, prompt improvement has been demonstrated in patients with fatty liver who are given relatively meager, unsupplemented, well-balanced diets (50 gm. protein, 1600 calories daily).[64, 65] Thus nutritional factors are more positively incriminated in the therapy of fatty liver than in the other types of acute hepatocellular injury mentioned.

Acute Liver Disease

Management of patients with acute hepatocellular injury is based on the manifestations of disease and not on etiology. Similar approaches to therapy thus apply to patients with viral, drug-induced, or chemical-induced hepatic injury, or with hepatic dysfunction associated with alcoholism or secondary to systemic disorders. Approach to managing patients with acute liver disease is outlined briefly, using viral hepatitis as a prototype.

Patients with viral hepatitis often experience anorexia, nausea, vomiting and diarrhea during the acute phase. Food and fluid intakes are limited, and losses of fluid and electrolytes are entailed. Nutritional deficits due to inadequate intakes for short periods are not serious, but jeopardy may result from dehydration and electrolyte imbalance. Accordingly, priority is given to correcting these with appropriate intravenous solutions containing glucose and electrolytes.

Even when symptomatic, most patients with hepatitis consume some food, particularly if it can be provided in small bland feedings. Ten per cent solution of glucose in water is given intravenously as a source of calories if oral intake falls below 15 to 20 calories per kg. per day daily for more than a few days. B-complex vitamins are added to the infusions if all or a significant fraction of total calories is given as glucose parenterally. As symptoms subside, food is provided to achieve as soon as possible an intake of 25 to 30 calories per kg. per day, and 0.5 to 1.0 gm. protein per kg. per day divided into four to six small, well-balanced meals. Dietary fat is restricted during the period of cholestasis, while bile pigment excretion into gut is limited. This is done to control symptoms of gastrointestinal intolerance, and not because fat is harmful. Diet fat content is increased as soon as bile pigments appear in the stool. Food intake is then gradually increased to tolerance until about 1.0 gm. protein per kg. per day, and 35 to 40 calories per kg. per day are achieved. Food is permitted ad lib if this quantity is consumed and tolerated. Patients are not force fed. Supplementary vitamins or other specific nutrients are not prescribed.

If the prothrombin time is prolonged, 10 mg. of water-soluble vitamin K derivative is given intramuscularly daily for 3 days to insure that vitamin K deficiency secondary to cholestasis and steatorrhea is not contributory. Hypoprothrombinemia is usually due to hepatocellular damage and inadequate prothrombin synthesis, and vitamin K has no

effect. Sometimes, however, hypoprothrombinemia is partially corrected by this therapy. Vitamin K is not given indefinitely if a therapeutic response is not demonstrated.

Nutritional Problems and Etiology. The incidence, severity, and complexity of management problems presented by patients with acute hepatocellular disease differ from patient to patient, depending upon the etiology.

Encephalopathy, fluid retention, renal failure, and nutritional deficiency diseases occur at low rates of incidence in patients with viral hepatitis. However, during the acute phase of the illness, force feeding of protein, excessive administration of salt, or overzealous use of glucose solutions may precipitate these complications. A few patients have persistence of symptoms and exhibit progressive or fulminant courses. Indications of the latter include onset, singly or in combination, of encephalopathy, ascites and edema, oliguria and renal failure, episodes of hypoglycemia, and bleeding tendencies. When these intervene, protein, salt, and water intakes are adjusted as described later. Careful attention to diet gains the time required for subsidence of the acute hepatocellular injury, and onset of repair and regeneration of liver.

Nutritional problems related to drug-induced hepatocellular injury or cholestasis or both are comparable to those outlined for patients with viral hepatitis, and management is similar. Encephalopathy, fluid retention, and renal failure are also uncommon. However, as with viral hepatitis, a few patients demonstrate rapidly deteriorating and fulminating courses.

Acute alcoholic hepatitis differs from infectious or drug-related hepatitis with regard to histologic features and clinical course.[37] Anorexia, nausea, abdominal complaints, weakness, and diarrhea often persist for weeks or months. Liver function tests are grossly deranged. Fever and polymorphonuclear leukocytosis are characteristic. Symptoms and findings may worsen in spite of abstinence, rest in the hospital, and supportive nutritional therapy. Recovery takes place slowly over weeks or months, when it occurs. Prognosis is grave if improvement is not evident within a few weeks. Those with persisting disease almost inevitably deteriorate nutritionally. In addition, they often initially have or eventually develop encephalopathy, ascites, edema, electrolyte imbalance, renal failure, and gastrointestinal bleeding. They must be carefully monitored for early indications of any untoward event so appropriate adjustments can be made in the treatment regimen.

Providing these patients with consistently adequate supportive nutritional therapy presents a real and continuing challenge. Overt vitamin deficiency diseases and serious derangements of hydration and electrolyte balance, especially hypokalemia, are often evident at the time of admission to the hospital. Many patients exhibit hematologic abnormalities due to folic acid deficiency. Prompt therapy with vitamins, fluids, and electrolytes, orally or parenterally or both, is mandatory.

Patients with acute alcoholic hepatitis are not force fed, since many develop encephalopathy, ascites and edema, and hyponatremia from excessive quantities of protein, salt, and water, respectively. On the

other hand, support of nutrition is not abandoned. We strive to provide at least 0.5 gm. of protein and 25 calories per kg. per day, utilizing parenteral glucose solutions to supplement caloric intake, if necessary. Fat is not restricted unless eating fat causes symptoms or aggravates diarrhea. Vitamin K is given parenterally to insure that deficiency is not contributing to hypoprothrombinemia. As in other patients with hepatocellular disease, giving vitamin K usually does not affect the prothrombin time.

Alcoholics may present with no symptoms or findings suggesting hepatic disease, although fat content is increased in liver tissue obtained by biopsy.[24, 50] Others with fatty liver have only tender hepatomegaly and bromsulfonphthalein retention. In addition, some have jaundice, and elevated serum alkaline phosphatase levels. Serum albumin and globulin levels are often normal. Hypoprothrombinemia is seldom severe, and serum enzyme levels may be normal or slightly increased. Fever and leukocytosis are not characteristic. Patients with fatty liver may be symptomatic from the consequences of gastritis, alcohol withdrawal, etc., when admitted to the hospital. They also often require hydration, correction of electrolyte imbalance, and vitamin therapy. The clinical course of patients in whom fatty liver is the dominant lesion is considerably more benign than that outlined for acute alcoholic hepatitis. Subjective symptoms and hepatic tenderness subside and appetite returns after a few days. Abnormalities of liver function may return to normal in a week or two; liver fat content usually becomes normal in 4 to 6 weeks. The prognosis is excellent, for the incident, at least. Patients with fatty liver seldom develop encephalopathy, ascites, edema, or renal functional failure. A small number (10 to 15 per cent) may have ascites and edema initially. This responds promptly to dietary sodium restriction. Problems of dietary management and modification are few, and restrictions are seldom needed. Patients with fatty liver are allowed to eat ad libitum as soon as they are able.

Chronic Hepatic Disease and Complications

Patients with uncomplicated hepatic cirrhosis may be relatively asymptomatic, eat well, and have no nutritional problems. Indeed, some such patients are well nourished. Diet ad libitum is recommended in these cases. Vitamin supplements are not prescribed. Complications associated with chronic cirrhosis are commonly related to intercurrent incidents which affect metabolic balances, or to terminal hepatic decompensation. They may become evident relatively rapidly with fulminant and more insidiously with persisting or progressive hepatocellular disease. Dietary manipulations are employed to control hepatic encephalopathy, ascites and edema, and renal functional abnormalities. The nature and severity of the complication determines the type and degree of dietary alteration required.

HEPATIC ENCEPHALOPATHY. Propensity to develop encephalopathy, stupor, or coma does not always correlate closely with clinical and laboratory findings. For example, some patients with overt evidences of acute or chronic hepatic disease tolerate protein well, and others with

relatively asymptomatic cirrhosis do not. Sometimes the onset of encephalopathy is a first indication that liver disease exists. There is no sure way to accurately estimate tolerance for protein, short of clinical trial. Since tolerance varies considerably from patient to patient, and in a given patient from time to time, one initial aim in managing cirrhotic patients without encephalopathy is to establish tolerance for protein. About 25 to 30 calories and 0.7 gm. protein per kg. per day are initially provided. This amount of protein is sufficient to achieve nitrogen equilibrium or positive nitrogen balance, but low enough to minimize the risk of hepatic encephalopathy. Increments of 10 to 15 gm. protein and 200 to 300 calories daily are added at intervals of 5 to 7 days if neuropsychiatric symptoms do not intervene. An attempt is made to achieve total intakes of about 1 gm. protein and 35 to 40 calories per kg. per day. Larger amounts of protein and calories are not needed to allow for improvement in hepatic function and nutritional status.[11] Increasing dietary protein intake above this amount entails increasing risk of inducing hepatic coma.

Protein intake is decreased to 25 to 35 gm. daily if on the diet initially prescribed *early* signs of hepatic encephalopathy occur. Orally administered neomycin is added to the regimen if 35 gm. daily (0.5 gm. per kg.) is not tolerated, since this level of protein is near the estimated minimal requirement for maintenance. Complete restriction of dietary protein intake is applied in patients with encephalopathy manifested by stupor or coma. Calories in the largest amount possible are furnished as carbohydrate and fat orally, or as glucose parenterally. A diet virtually devoid of protein should not be continued any longer than absolutely necessary. Often minimal protein feedings can be reinstituted after several days, especially when coma is precipitated by some reversible cause. The protein is often better tolerated if offered in multiple small bland feedings instead of the usual three. Feeding of protein is gradually resumed as reversal of stupor or coma is evident. While dietary protein is being added by increments, treatment with neomycin is continued. Consideration is given to gradually withdrawing neomycin therapy when intakes of 0.50 to 0.75 gm. protein per kg. per day are achieved.

Some patients with advanced hepatic cirrhosis, especially after surgical construction of portal systemic shunts, require extreme degrees of dietary protein restriction (15 to 20 gm. daily) indefinitely. This restriction ultimately puts them in jeopardy from protein malnutrition. On the other hand, some such patients do surprisingly well for long periods, considering the limitation of the diet. Fortunately most patients with chronic recurring or persistent encephalopathy can be controlled by dietary manipulation or other medical therapy.

A few patients with recurring or persisting encephalopathy requiring rigid control of protein intake have good appetites which lead to ingestion of more protein than they are able to metabolize adequately. These patients are difficult to manage, since their mentation is often limited and their behavioral patterns are aberrant. Someone must provide custodial care and supervise food intake.

Dietary protein restriction also incidentally entails restricting

potassium intake, and neomycin therapy and bowel cleansing (catharsis and enemas) induce potassium losses. Thus generally accepted therapeutic measures for patients with hepatic coma tend to limit intake and induce or aggravate existing potassium deficits. Cirrhotic patients have limited body potassium stores,[9] and losses often result from nausea, vomiting, diarrhea, and use of diuretic agents. In addition, some patients exhibit renal tubular acidosis and renal potassium wasting.[78] For these reasons potassium deficiency occurs commonly and is sometimes involved in the pathogenesis of coma.[6, 31, 79] Deficiency of this cation due to any cause may induce hepatic encephalopathy in susceptible patients by affecting renal ammonium metabolism and altering pH gradients favoring diffusion of ammonia into cells.

Supplementation is indicated if potassium deficiency is established by medical history, decreased blood level and appropriate electrocardiographic change. If necessary, potassium salts can be given slowly intravenously, but oral supplements are preferred. Oral supplements can be given in large quantity (100 to 150 mEq. daily in divided doses) without danger if urinary output is adequate (> 1000 ml. per day). In patients in whom hepatic encephalopathy is related to potassium deficit, favorable clinical response to potassium chloride therapy is usually evident in a day or two, and obvious in 3 to 5 days.

ASCITES AND EDEMA. Multiple factors contribute to the formation of ascites and edema in patients with hepatic disease. However, whatever the pathogenetic factors involved, fluid retention is readily conditioned by the sodium content of the diet.[19, 21, 34, 49, 70] Patients with liver disease, given salt and water, expand extracellular fluid volume isotonically, gain body weight, and develop ascites and edema. The rate of weight gain is directly proportional to the sodium intake.[34] These patients are in positive sodium balance while collecting fluid and excreting minimal amounts of sodium in the urine. They are brought into balance by restricting sodium intake.

Rigid restriction of sodium intake is usually required for cirrhotic patients. Patients with ascites and edema are treated initially with a diet containing 250 mg. sodium, 50 gm. protein, about 2000 calories, and 1500 ml. of fluid daily. The sodium-restricted diet is prescribed even though serum sodium concentration is moderately decreased (125 to 130 mEq. per L.). Further accumulation of fluid inevitably results if intake is not restricted. Symptomatic hyponatremia requiring correction with hypertonic salt solution and water restriction occurs only rarely, and then usually in relation to some precipitating event. A significant number of patients given the sodium-restricted diet demonstrate spontaneous diuresis.[26] This may occur within a few days, but more often within a few weeks. There is no sure way to predict whether or not diuresis will occur, or when. In general, patients with reversible liver disease such as fatty liver or patients in whom onset of fluid retention correlates with excessive intake of salt are likely to respond favorably. Patients with persisting active disease (active chronic hepatitis, alcoholic hepatitis) and those with chronic cirrhosis who are symptomatic, hyponatremic, hypoproteinemic, and undernourished are less likely to

demonstrate a diuresis. In any event, the most important aspect of long-term as well as short-term management of patients with ascites and edema is the consistent intake of a well-balanced diet restricted in sodium content. Chronic cirrhotics treated for prolonged periods of time with special diet alone may demonstrate improvement in nutritional status, hepatic function, portal hypertension, and tolerance for salt.[14, 34]

Sodium depletion seldom develops in patients with ascites and edema who are maintained for prolonged periods on diets rigidly restricted in sodium content. Those who present with moderate hyponatremia may tend to correct serum sodium concentration over a few weeks, even though dietary sodium is restricted. In others this paradoxical increase in serum sodium concentration may occur insidiously after weeks or months.[19, 34] Hyponatremia which persists or becomes progressive in the absence of demonstrated fluid and electrolyte losses usually indicates intolerance to water and a relatively grave prognosis.[80, 84, 85]

Consideration can be given to liberalizing sodium intake when ascites and edema are no longer evident.[26] Even then the sodium restricted diet should be continued for several additional weeks at least, and preferably for a month or two. Testing is done gradually by allowing a daily increment of about 500 to 1000 mg. of sodium in the diet. An additional increment of 1000 mg. is allowed after a week or 10 days if body weight did not increase and ascites and edema did not recur. Sodium intake is again restricted at any point that weight gain or fluid retention is noted. Sodium intake is not liberalized beyond 2500 mg. daily. This level entails only avoiding the use of highly seasoned foods and the use of salt in cooking and at table; it does not necessitate purchase of special dietary foods.

Renal Function. Patients with acute, progressive, or advanced chronic hepatic disease often do not handle water loads normally.[59, 80, 84, 85] Accordingly, in prescribing fluid intakes a balance must be achieved between providing sufficient fluid intake to insure reasonable urine flow rates, yet not forcing fluids to induce body weight gain and dilutional hyponatremia. We initially prescribe 1500 to 2000 ml. daily. If this volume is tolerated, no effort is made to increase the intake above 2000 ml. (assuming reasonable environmental conditions). If weight gain and decreasing sodium concentration are evident, fluid intake is sequentially restricted until this unfavorable trend ceases and reverses. Often, persisting or progressive hyponatremia indicates insidiously developing renal functional impairment. More overt indications include persisting oliguria, azotemia, creatinemia, and hyperuricemia. Consideration must first be given to the possibility of potential reversibility, when renal failure is evident. Complications that may have resulted in dehydration or hypotension must be evaluated and promptly managed by appropriate means. Because of the high incidence of infection, dehydration, electrolyte abnormalities, bleeding, etc., which they suffer, these patients are highly predisposed to developing acute tubular necrosis. If this diagnosis is established, strict control of fluid, electrolyte, and protein intake is instituted.

Other patients with severe acute or advanced chronic liver disease

demonstrate "spontaneous" renal functional failure that is not related to any significant histologic renal abnormality. Patients with "spontaneous" renal failure should be managed as if they had acute tubular necrosis.[80, 84, 85] Serious decreases in serum sodium concentration often result from excessive water administration.[80] Sodium salts are not usually given unless signs and symptoms of acute dilutional hyponatremia are present and serum concentration is less than 125 mEq. per L. In most instances restriction of fluid intake is the treatment of choice. Intake is usually restricted to about 500 ml. in excess of the previous 24 hour urine volume. Modification of intake may be required if enteric and sweat losses are involved. The aim is induction of negative water balance, progressive decrease in body weight, and increase in serum sodium concentration.

CHANGING TOLERANCES

Changing tolerances for dietary protein, salt, and water occur in patients with acute and chronic hepatic disease.[26, 33] Those becoming rapidly ill may demonstrate rapidly developing intolerance to these constituents of the diet. Patients with chronic or progressive diseases may develop intolerances insidiously over periods of months or even years. Contrariwise, patients with subsiding acute diseases, quiescent persisting disease, or improving chronic disease may demonstrate increasing tolerances. For example, protein or salt intakes which were initially excessive may be tolerated well when hepatic disease improves. Given intakes may also become excessive when intercurrent complications such as infection, surgical procedures, gastrointestinal bleeding, or electrolyte abnormalities (particularly potassium deficiency) intervene. Patients for whom portal systemic shunts are constructed often have decreased tolerance for protein postoperatively, especially in the immediate postoperative period. Although improving tolerances may be accompanied by clinical and laboratory evidences of improving hepatic function, these favorable changes may occur in patients who are apparently stable. Sometimes tolerance can be determined only by careful clinical trial at selected intervals. Dietary needs with regard to restriction or liberalization are determined by the physician's sequential evaluation of individual patients. This must be done day by day in those who are acutely ill, and month by month in those who are chronically ill.

Medical management of patients with acute and chronic hepatic diseases includes the application of established principles of nutrition. Proper application of these principles depends much upon the evaluation of individual patients with special reference to the early detection of encephalopathy, fluid retention and renal dysfunction which are amenable in some measure to dietary manipulation. These complications often relate to progression of liver disease or to intercurrent incidents which affect liver function adversely. At other times they result from excessive metabolic loads, rather than hepatic decompensation. Increasing tolerances for protein, salt and water often relate to improvement in liver

function. In some cases, however, decreasing or increasing tolerances occur in patients who are apparently stable. Prescription of their dietary needs depends entirely upon clinical acumen. The physician must provide sufficient protein and calorie intakes to insure healing of the diseased liver and general nutritional rehabilitation, and at the same time apply restrictions when necessary to control complications related to dietary excesses. Severe dietary restrictions must not be imposed unnecessarily.

The concept of tolerances which may change for the better or for the worse must be fully appreciated so the balance between what is prescribed and the patient's ability to handle the prescribed quantities is maintained near equilibrium. Only in this way are patients ill with liver disease and its complications provided with optimal nutritional therapy.

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Nutrition and Endocrine Disease

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The maintenance of optimum nutrition in man depends primarily on normal endocrine function and an adequate diet. The endocrine system, by virtue of the control exerted by hormones on metabolic processes in general, regulates the requirements for various nutrients. Although the development of nutritional disturbances in patients with endocrine disease, despite ingestion of an adequate diet, emphasizes the critical role of the endocrine glands in this relationship, diet, under certain circumstances, can exert an important modifying influence. Since the metabolic abnormalities that occur with endocrine disease are ultimately expressed in alterations in the tissue content of the body, the accompanying nutritional disturbances will be discussed in terms of changes in body composition. Because of space limitations, we have confined our discussion to body compositional changes that occur in patients with pituitary, thyroid, and adrenal disease. For the purposes of convenience, endocrine-nutrition relationships will be considered from two aspects: (1) the effects of endocrine disease on nutrition and (2) the effects of nutrition on endocrine function.

Although in vitro systems have been particularly helpful in defining the specific metabolic effects of hormones, proper interpretation of metabolic and nutritional abnormalities that develop in endocrine disease requires knowledge of the effect of the hormone in the intact animal. It is now apparent that the metabolic alterations that occur in vivo as a result of a specific hormonal abnormality often represent the

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net effects of the interaction of one or more additional hormones. Appreciation of this fact is of critical importance in understanding the changes that occur in body composition in endocrine disease.

GROWTH HORMONE

In contrast to many other hormones with specific target organs or tissues, growth hormone stimulates the growth of almost all tissues. The administration of human growth hormone to normal subjects produces prompt changes in the intermediary metabolism of carbohydrate, protein, and fat, and in mineral balance.[30, 39, 40, 46, 77, 78] Growth hormone promotes the mobilization of free fatty acids from adipose tissue by stimulation of a specific lipolytic system. A number of studies which consider the temporal aspects of free fatty acid release and the requirement for de novo protein synthesis indicate that this system is separate from the "hormone-sensitive lipase" stimulated by catecholamines.[105] Free fatty acid levels rise slowly but are clearly elevated within 4 hours. The effects of a single large dose of growth hormone on insulin secretion can be observed within 12 to 24 hours. Blood glucose concentrations may or may not be changed, depending upon the dose of hormone utilized, but fasting plasma insulin concentrations and their response to glucose challenge are augmented.[66] The effects of growth hormone on pancreatic beta-cell function may be both direct and indirect. Inhibition of peripheral glucose utilization due to a specific effect of growth hormone on glucose transport[112] or free fatty acid mediated inhibition of glucose uptake[80] or both results in peripheral insulin resistance and elevated blood glucose concentrations which may secondarily increase insulin release. In addition, growth hormone may have a specific beta-cytotrophic effect.[11] However, regardless of its mechanism, hyperinsulinemia is a concomitant of excessive growth hormone secretion or administration.[21, 50, 60, 66, 93]

Following the administration of growth hormone, there is a decrease in urinary and fecal nitrogen excretion and positive nitrogen balance.[30, 39, 40, 46, 77, 78] There is also a concomitant retention of chloride, phosphorus, potassium, and sodium, but paradoxically, calcium balance becomes negative. The administration of growth hormone to animals stimulates amino acid uptake by tissues and protein synthesis,[51, 61] and it seems reasonable to assume that growth hormone has similar effects in humans. The amount of nitrogen and phosphorus retained during the acute administration of growth hormone to humans is greatly in excess of that required for rapid growth, and a great percentage is thought to be converted to labile protein stores which are mobilized upon discontinuation of the hormone. However, the administration of human growth hormone for several weeks is associated with a gradual return of nitrogen excretion to normal,[40] a point of some importance when considering the effects of excessive growth hormone secretion. The combined effects of growth hormone on intermediary metabolism can best be described as anabolic.[77] The energy for growth hormone–stimulated protein synthesis

is provided by augmented fat breakdown and metabolism. In addition, the provision of adequate substrate in the fasted state in the form of free fatty acids and ketone bodies, to satisfy energy requirements and limit glucose utilization, diminishes the need for gluconeogenesis and thus preserves body protein stores. It has been proposed, from patterns of insulin and growth hormone release in response to carbohydrate and protein feeding, that the phase of combined insulin and growth hormone secretion, which occurs 2 to 4 hours after a meal, promotes protein synthesis.[79] Optimum protein synthesis in the intact animal also requires the presence of insulin, and it is unlikely that the effects of growth hormone can be maximally exhibited in the absence of insulin.[61]

Acromegaly

It is obvious from gross inspection that nutrition and body composition are significantly altered in acromegaly. Unfortunately, except for measurements of skin fold thickness[7, 109] and a few compositional studies[43, 44] there are no in vivo or postmortem studies to quantify body compositional changes. Many of the classic features of acromegaly are due as much to soft tissue thickening as to bony overgrowth. The increased soft tissue thickening can be confirmed by measurements of skin fold thickness as well as radiographically.[97] The subcutaneous tissues are thickened by replacement of fat with non-inflammatory connective tissue which is morphologically and chemically normal.[48] Splanchnomegaly and a generalized increase in body connective tissue have been well documented in autopsy studies of patients with acromegaly.[17] Although profound alterations in fat content might be expected, as a result of the lipolytic action of growth hormone, comments on the quantity and distribution of adipose tissue in patients with acromegaly are scarce.

Isotopic studies of body composition in acromegaly have revealed significant alterations in total body water, its partition between the intracellular and extracellular compartments, and in exchangeable sodium and potassium.[43, 44] Total body water, expressed either as a percentage of body weight or on the basis of surface area, is significantly increased in patients with acromegaly.[44] However, extracellular water is increased to a greater degree than is intracellular water. The exchangeable body sodium (Na_e), expressed in reference to body weight, surface area, or total body water, is also significantly increased.[44] Although the exchangeable body potassium (K_e) is increased in acromegaly, it is less than normal when expressed on the basis of body weight.[43] Since the relationship between intracellular water and K_e is considered to be constant, these findings indicate that there is a greater increase in extracellular water relative to body cell mass in acromegaly. Estimates of several parameters of body composition can be derived from the measurements of total body water and K_e in patients with acromegaly. The "body cell mass," or metabolically active portion of the body, calculated from the K_e and the factor[67] of 8.33, is increased in acromegaly, but it is not significantly different from normal when expressed relative to body weight. Similarly, calculations of "lean body mass" (fat-free body) from the total

body water and a coefficient of hydration[67] of 0.72 results in estimates of body fat relative to body weight that are within normal limits. However, the measurements of intracellular and extracellular water indicate that the coefficient of hydration in acromegaly may be greater than 0.72. Therefore, use of the factor 0.72 would give spuriously elevated estimates of lean body mass and would underestimate total body fat. These data indicate that in a heterogeneous group of patients with acromegaly in various stages of activity, body fat stores are probably normal.

Whether or not metabolically active tissue increases in acromegaly at a rate commensurate with supporting structures, such as bone and connective tissue, can be obtained from the relationship[67] between K_e and "fat-free solids" (FFS = B.Wt − [TBW + TBF]), where TBW and TBF equal total body water and total body fat respectively. The ratio of K_e to FFS in a healthy adult[67] ranges from 208 to 242 mEq. per kg. A disproportionate increase in extracellular solids or a decrease in the metabolically active portion of the body would produce a lower K_e/FFS. The mean K_e/FFS for 12 acromegalic patients, derived by us from the data of Ikkos and co-workers[43, 44] was 188 mEq. per kg. ± 6.9 (SEM), a value considerably lower than normal and indicative of a greater increase in supportive tissue than in metabolically active tissue in acromegaly. Although body overgrowth and skeletal hypertrophy are common concomitants of human and experimental acromegaly, there are no estimates of skeletal weight in patients with acromegaly. Moore has derived a formula for prediction of dry fat-free bone from the K_e and K_e/FFS ratio.[67] Estimates of dry fat-free bone in 23 normal males and 7 normal females ranged from 4.05 to 6.95 kg. by this technique.[67] Our calculations of the dry fat-free bone in the 12 acromegalics studied by Ikkos et al. ranged from 4.70 to 10.19 kg., with a mean of 7.35 kg ± 0.45 (SEM). While this increment in skeletal weight may seem relatively unimpressive, one must remember that despite skeletal overgrowth, osteoporosis occurs commonly in acromegaly,[3] and this would tend to minimize the changes. However, when expressed on the basis of fat-free body weight, the skeletal weight was 11.95 per cent, a value only slightly greater than the 10.3 per cent in normal subjects. While these studies in general indicate that enhanced nitrogen retention has occurred in acromegaly, there is no information concerning the long-term effects of excessive growth hormone secretion on nitrogen balance. Raben has estimated that nitrogen storage during the period of rapid growth for the Alton giant was 0.6 to 0.8 gm. per day, in comparison to a normal storage rate of 0.2 to 0.3 gm. per day.[77]

Increased metabolism has been commonly associated with acromegaly in the presence of normal thyroid function.[45] The question arises as to whether this is a spurious increase resulting from an underestimation of body surface area from height-weight tables in a patient with kyphosis, or whether it results from a true increase in metabolic rate. When oxygen consumption is related to K_e, the patient with acromegaly has a rate of oxygen consumption that is greater than normal at any given K_e, indicating that the basal metabolic rate is truly increased.[45]

Important information concerning the long-term nutritional effects

of excessive secretion of growth hormone in humans can be obtained from dissection and carcass analysis studies of animals treated chronically with anterior pituitary extracts or growth hormone. In both dogs[76] and rats,[56] administration of growth hormone increases total body weight and length, and except for adipose tissue, produces a generalized increase in the weights of most tissues and organs. The chronic administration of anterior lobe pituitary extract to a dog for 70 weeks produced a characteristic acromegalic animal with most of the features of the disorder in humans.[76] There was a generalized increase in skin thickness, characteristic bony overgrowth, and splanchnomegaly. Despite the increase in muscle mass, weakness, poor muscular coordination, and laxity of muscles and ligaments were observed during the period of rapid growth. In contrast to the healthy-appearing bright red skeletal muscles of non-treated dogs, the voluntary muscles of the treated animal were dull and gray, suggesting increased quantities of connective tissue. The combined organ weights constituted approximately 8 per cent of the total weight of the treated animal, as compared to 5.5 per cent of the total weight of the control animal, thus emphasizing the splanchnomegaly produced by growth hormone. In addition, subcutaneous and omental fat was completely absent. This finding may be due to the ease with which frank diabetes mellitus is induced in the dog,[4, 111] and as indicated by isotopic composition studies, it is not representative of acromegaly in humans. Rats chronically treated with growth hormone gain weight at approximately twice the rate of control animals.[56] In addition to the acceleration of growth, carcass analysis revealed that water, protein, and ash constituted a greater proportion, and fat a smaller proportion, of the weight gained when treated and pair-fed control animals were compared. During the period of observation, rats treated with growth hormone gained 237 gm. of protein and 162 gm. of fat, while control animals gained only 96 gm. of protein and 281 gm. of fat. These changes emphasize that the effects of growth hormone on protein synthesis and fat mobilization which are seen acutely are reflected chronically by body compositional changes in which lean body mass increases at the expense of adipose tissue.

Growth hormone, probably because of its ability to produce peripheral insulin resistance, is both diabetogenic and insulinogenic in humans.[21, 50, 59, 60, 66, 93] The administration of human growth hormone to normal subjects raises plasma insulin levels and augments the insulin response to glucose challenge.[66] If a sufficiently large dose of growth hormone is administered, glucose tolerance will be impaired, despite hyperinsulinemia.[66] In hypophysectomized diabetic subjects, growth hormone exacerbates the diabetes and produces hyperglycemia and ketosis.[59] Although diabetes mellitus occurs in only 25 to 30 per cent of patients with acromegaly, fasting hyperinsulinemia is a common concomitant, occurring in 30 to 70 per cent of the cases.[21, 50, 60, 93] Because insulin response to glucose in the non-diabetic acromegalic is prompt and exaggerated, while that of the diabetic acromegalic is delayed and retarded, and because 20 to 25 per cent of the non-diabetic population displays the latter type of response, Luft has postulated that diabetes occurs

only in patients who are low insulin responders prior to the onset of their disease.[60]

Although growth hormone is capable of stimulating the synthesis of most cellular constituents, it is quite likely that the compositional changes produced by excessive growth hormone secretion are a result of its interaction with insulin. The metabolic changes which accompany the administration of growth hormone to dogs support the proposal that the interaction between growth hormone and insulin is important.[76] In the early stages, administration of growth hormone to dogs produces positive nitrogen balance and weight gain despite peripheral insulin resistance. The implication is that this is a phase in which insulin secretion increased appropriately, and the metabolic effects are a result of the combined actions of growth hormone and insulin. Continued administration, however, induced hyperglycemia, glucosuria, and ketonuria similar to that observed in juvenile diabetics, and the growth rate decreased suggesting that an inadequate insulin response has now modified the growth-promoting effects of growth hormone. Unfortunately, in acromegaly no correlation between the clinical features of the disease and carbohydrate tolerance or insulin levels can be made.[21]

Hypopituitarism

Although gross nutritional and body compositional changes might be expected in adult hypopituitarism, there appears to be disagreement concerning the incidence and degree of inanition. Emaciation is not a cardinal feature of Sheehan's syndrome.[91] In an analysis of the nutritional status of 88 postpartum hypopituitary patients at death, Sheehan observed that only 30 per cent could be considered emaciated or thin, in contrast to 42 per cent of patients dying from other causes. Furthermore, analysis of the nutritional status of the patients 6 months prior to death provided no support for the commonly held opinion that hypopituitarism is characterized by emaciation. In contrast, 65 per cent of 101 verified cases of Simmond's disease compiled from the literature by Escamilla were cachectic.[27] The reason for this discrepancy is not clear and may depend upon the degree of hypopituitarism in Sheehan's patients. Organ weights from 32 autopsies of patients with panhypopituitarism were significantly less than normal.[91]

Unfortunately, there are no metabolic or body compositional studies that we are aware of in adult patients with hypopituitarism. In terms of the action of growth hormone on intermediary metabolism, it seems reasonable that lean body mass would be decreased relative to adipose tissue, even in the wasted individual. Such a conclusion is supported by studies of children with isolated growth hormone deficiency[75, 100] and hypophysectomized animals.[56] On the other hand, the exact role of growth hormone in the adult has not been defined. It appears that a deficiency of growth hormone does not impair fat or protein mobilization in starvation[64, 89] but in ateliotic adult dwarfs it may be necessary to prevent hypoglycemia.[61] The alterations in nutrition and body composition that occur in hypopituitarism are frequently the result of multiple hormone deficiencies, and discussion of these changes in terms of deficits of single hormones may not be accurate.

The effect of hypophysectomy on the nutrition and body composition of rats provides insight into the changes that probably occur in patients with hypopituitarism. After hypophysectomy in rats, food consumption decreases by approximately 50 per cent, and weight loss ensues.[56] It is possible that failure of weight loss to be a constant finding in human hypopituitarism in contrast to animals is due to the fact that food intake in man is regulated by the ritual of eating as much as or more than it is by physiologic need.[88] When the caloric intake of normal rats is restricted to a degree comparable to that ingested spontaneously by the hypophysectomized rats, weight loss occurs at the same rate.[56] In hypophysectomized rats, protein reserves are mobilized and utilized as a source of energy with little accompanying loss of adipose tissue. During the period of weight loss in the hypophysectomized rat, water, fat, and protein account for 69, 14, and 13 per cent respectively of the loss. In contrast in the pair-fed control animals, protein was conserved and fat was utilized as the primary energy source, water and fat constituting 58 and 43 per cent respectively, and protein none of the tissue lost. Thus in rats with hypopituitarism, fat is preserved at the expense of body protein. Preservation of body fat is also observed in children with isolated growth hormone deficiencies.[75, 100]

Considerably more is known about the effects of hypopituitarism on nutrition and body composition in children than in adults. The most obvious manifestation of growth hormone deficiency in the child is growth retardation. Other body tissues, however, are also affected by the deficiency as indicated by the measurement of skin-fold thickness,[75, 100] and urinary creatinine excretion.[34] In children with growth hormone deficiency, skin-fold thicknesses, relative to age, are greater than the 50th percentile,[75, 100] indicating an increase in subcutaneous adipose tissue. Diminished muscle mass is reflected by subnormal urinary creatinine excretion[34] and studies of muscle cell number and size.[13] In hypopituitary dwarfs, absolute muscle cell numbers are significantly decreased relative to age.[13] However, cell numbers are appropriate when related to total body water or lean body mass, or when considered in relationship to the reduction in linear growth. Most hypopituitary dwarfs also have small muscle cells relative to body size.[13]

Treatment of growth hormone–deficient children with human growth hormone results in the retention of nitrogen, sodium, potassium, and phosphorus.[11, 110] Although urinary calcium is invariably increased by administration of growth hormone,[30, 39, 40, 46, 77, 78] it has been stated that the net calcium balance becomes positive due to enhanced gastrointestinal absorption.[40, 77]

The effects of human growth hormone are greater and more prolonged in children with growth retardation due to growth hormone deficiency, than in children with short stature due to other causes.[75, 100] In addition, children with growth hormone deficiency demonstrate a phase of "catch-up growth" during the first 3 to 6 months, during which the rate may approach 15 to 20 cm. per year.[75, 100] An adequate increase in linear growth rate in response to human growth hormone is almost always accompanied by a decrease in subcutaneous fat;[75, 100] however, body weight does not decrease proportionately, indicating a commen-

surate increase in muscle mass. After 8 months of treatment with human growth hormone, urinary creatinine excretion is increased,[34] reflecting the increase in muscle cell number, size, and mass.[13] However, the increase in muscle mass is greater than that in linear growth, indicating that the growth of the cellular phase is stimulated to a greater extent than that of bone and cartilage.

Although it has not been clearly defined, insulin, as stated, probably plays a permissive role in the stimulation of growth by growth hormone. In growth hormone–deficient children, fasting and glucose or arginine-stimulated insulin values are significantly lower than those of normal children, and treatment with human growth hormone results in concomitant improvement of insulin secretion.[63]

Although there may be no metabolic manifestations of growth hormone deficiency in adults, hypoglycemia may be a distressing and serious problem in children. Recurrent hypoglycemia occurs in approximately 50 per cent of children with isolated growth hormone deficiency and in 100 per cent of children with combined deficiencies of corticotropin and growth hormone.[32] The hypoglycemia occurs in the presence of low plasma insulin concentrations[63] and is not due to a failure to provide sufficient substrate to satisfy energy requirements, since fat mobilization proceeds normally, but may be due to continued utilization of glucose by muscle.[89]

THYROXINE

Although the effects of thyroid hormone on oxygen consumption and metabolic rate have been known for many years, the mechanism by which thyroid hormone produces these changes is still not well defined. Furthermore, from a nutritional standpoint, studies of body composition in patients with thyroid disease have been infrequent, and conclusions concerning compositional changes must often be inferred from the known metabolic effects of thyroxine. Changes in appetite, intestinal absorption, metabolic rate, and the metabolism of carbohydrates, protein, and fat, contribute in varying degrees to the nutritional manifestations observed in patients with thyroid disease.

Hyperthyroidism

Despite increased caloric intake, the patient with hyperthyroidism is in negative energy balance and is often wasted and malnourished. The number of calories required to accomplish a given amount of work in hyperthyroidism may be twice the amount needed normally.[10] Although the appetite is usually (but not always) stimulated by hyperthyroidism, increased food consumption does not prevent the marked weight loss that accompanies this disorder. In advanced hyperthyroidism, the muscle wasting and decrease in body fat is so obvious that the conclusion that there must be gross alteration of body composition is inescapable. Whether subtle alterations in body composition also accompany mild hyperthyroidism is unknown, but it seems reasonable

that the changes would be qualitatively similar and differ only quantitatively from those observed in more advanced cases.

The regulation of protein synthesis by thyroxine is to a large degree dependent upon the amount of hormone present, and is optimum when thyroxine is present in physiologic concentrations. It has been suggested that the effect of thyroxine on oxygen consumption is mediated through regulation of protein synthesis, since the increased metabolic rate observed in thyrotoxic rats can be blocked by inhibitors of protein synthesis.[65] It is interesting that the stimulation of protein synthesis occurs only in those tissues—heart, kidney, and liver—which, with respect to oxygen consumption, are influenced by thyroxine.[65] It is difficult to develop a unified concept of the effects of thyroxine on protein metabolism because of the wide variety of experimental conditions under which studies have been performed. From a review of the literature, the conclusion that thyroxine stimulates both protein synthesis and degradation seems reasonable. In the euthyroid animal and in man, protein synthesis and degradation are balanced so that optimum levels of body protein are maintained. Whether protein synthesis is increased or decreased in hyperthyroidism cannot be determined from the literature.

Protein synthesis has been assessed in humans by measurement of ^{15}N-glycine incorporation into urinary urea, based on the assumption that protein synthesis is inversely related to the recovery of ^{15}N in the urine.[16] From a single study in which 100 micrograms of triiodothyronine was administered to one normal human volunteer after ^{15}N-glycine, it was concluded that protein synthesis was decreased.[16] However, other conclusions also seem reasonable, since the excretion of ^{15}N in the urine, as urea, is determined by the ^{15}N that is not incorporated into protein as well as that which is converted to protein and subsequently degraded. The results in this patient are therefore compatible with the concept that excessive thyroxine concentrations increase catabolism to a greater degree than anabolism, and thus mask the stimulatory effects of thyroxine on protein synthesis.

Similar reasoning has been utilized to explain the hypocholesterolemia that occurs in hyperthyroidism in the presence of increased cholesterol synthesis.[69] The induction of negative nitrogen balance by the administration of large doses of triiodothyronine to a normal human volunteer[16] and thyroid hormone to normal rats[86] demonstrates that the net effect of excess thyroid hormone on protein metabolism is catabolic. Administration of pharmacologic doses of thyroid hormone to normal obese subjects to accelerate weight loss results primarily in a loss of body protein.[54] Following therapy of thyrotoxicosis, exchangeable body potassium increases,[96] indicating restoration of lean body mass toward normal. In view of the above data, it would be predicted that a loss of lean body mass would be incurred in thyrotoxicosis.

Free fatty acids are the primary fuel of the fasting state. The mobilization of free fatty acids is accelerated by thyrotoxicosis.[18, 38, 81] Increased mobilization of fat would lead to the decreased fat stores which are observed clinically in thyrotoxicosis. It has been postulated that enhanced oxidation of fatty acids secondary to increased plasma levels may

be responsible for the increased oxygen consumption and hypermetabolism in thyrotoxicosis. However, inhibition of lipolysis and reduction of plasma free fatty acid concentrations by nicotinic acid does not alter oxygen consumption.[90] Therefore it seems likely that the increase in oxygen consumption is a direct effect of thyroxine.

Thyrotoxicosis is usually associated with a negative calcium balance, and hypercalcemia may be an occasional feature of the disorder.[3, 84] Urinary calcium excretion is increased,[3] and plasma calcium concentrations in one series averaged 0.5 mg. per 100 ml. higher than matched normal controls.[84] However, severe hypercalcemia and symptomatic bone disease are rare.[23] Although bone formation and resorption are increased in thyrotoxicosis, the resorptive phase predominates and skeletal changes indistinguishable from osteoporosis are observed.[1] The negative calcium balance and osteoporosis are reversed with treatment.

Unfortunately, there are essentially no published body composition studies which have been performed prior to and following therapy in patients with thyrotoxicosis. However, on the basis of the preceding discussion of the metabolic abnormalities that accompany this disorder, it seems reasonable to conclude that both lean body mass and fat are diminished.

Hypothyroidism

In hypothyroidism, oxygen consumption and the requirement of calories and other specific nutrients is decreased. It seems reasonable that body compositional alterations would not occur or would be minimized in hypothyroidism if food intake were adjusted to metabolic requirements. Neither weight loss nor obesity is a common clinical feature of hypothyroidism. Comparison of actual and theoretical body weights in 200 patients with spontaneous myxedema, by Plummer, revealed that 62 per cent were overweight and 38 per cent were underweight.[58] Body weight was inversely proportional to the severity of the myxedema. Those patients with basal metabolic rates below minus 28 were underweight after the initial acute period of "fluid" loss incurred by therapy, implying that the loss of body tissue in myxedema was masked by the accumulation of fluid. Hypothyroid children have been shown to have excessive total body water,[12] increased creatinine excretion,[14] and larger than normal muscle cells.[18] With therapy, there is a net loss of water and potassium from the cellular phase, a lowering of creatinine excretion, and a return to normal of muscle cell size.[18] This indicates a loss of muscle mass with therapy, and implies at least that the lean body tissue is not diminished by hypothyroidism. Negative nitrogen balance and greater loss of fat free tissue than of fat has been observed in two adults with myxedema treated with replacement doses of thyroid hormone,[7] suggesting that preceding lean body mass was normal or increased. Studies of ^{15}N excretion following the administration of ^{15}N glycine indicate that protein synthesis is decreased in patients with hypothyroidism.[7] However, the presence of a slightly positive nitrogen balance in patients with hypothyroidism implies that catabolism is decreased to a greater degree than is anabolism, the opposite of what occurs in hyperthyroidism.

As a result of decreased food consumption, thyroidectomized rats gain considerably less weight than force-fed thyroidectomized and pair fed normal rats.[30] In addition, the conversion of substrate to tissue is changed so that gross alterations in body composition occur. Carcass analysis reveals that body fat comprises 55 and 32 per cent respectively of the total weight gained by the force-fed and ad-lib fed thyroidectomized rats, but only 13 per cent of the weight gained by the normal ad-lib fed rats. In contrast, the gain in body protein is inversely related to the gain in fat, so that protein constitutes 10 and 16 per cent respectively of the weight gained by the force-fed and ad-lib fed thyroidectomized rats and 21 per cent of the weight gained by the ad-lib fed normal rats. From an overall standpoint, fat constitutes 38, 15, and 12 per cent, and protein 13, 18, and 21 per cent respectively of the total body weight of force-fed and ad-lib fed thyroidectomized rats and ad-lib fed normal rats. Increased body fat in hypothyroidism may be related to the permissive effects of thyroxine on lipolysis[33] and decreased mobilization of fatty acids from adipose tissue.

Thus, the results of the available information in animals suggests that the ingestion of food at a rate which existed prior to the development of hypothyroidism, or at a rate commensurate with metabolic requirements, may result in an increase in body fat and water with preservation of lean body mass. By extrapolation of these results to humans, it might be predicted that those patients who continued to consume their customary euthyroid diet would have the largest gain in adipose tissue and the greatest alterations in body composition, whereas those whose intake was adjusted to meet metabolic requirements would have only minor body compositional changes.

GLUCOCORTICOIDS

Glucocorticoids alter intermediary metabolism in a manner which increases or maintains the blood glucose concentration at the expense of body protein and fat. Glucose production is increased as a result of augmented synthesis of a series of enzymes in the gluconeogenic pathway.[101] The action of cortisol on body protein and fat also provides adequate quantities of substrate to satisfy the increased gluconeogenic requirements. Cortisol decreases protein synthesis and accelerates protein catabolism[12, 107] thereby increasing the availability of amino acids for gluconeogenesis. It also exerts a permissive effect of lipolysis in adipose tissue,[29, 33] which, in addition to providing free fatty acids for energy, increases the availability of glycerol, a by-product of lipolysis, for gluconeogenesis. Ordinarily, the effects of glucocorticoids on these processes are carefully coordinated so that homeostasis is maintained. Only when inadequate or excessive quantities of glucocorticoids are present is the delicate balance between these processes disturbed.

Glucocorticoid Excess

The weak fat lady described by Cushing in 1932 represents the more severe nutritional consequences of glucocorticoid excess and is easily

recognizable even by a layman. Although the patient with excessive secretion of cortisol is typically fat, this appearance represents the end-product of many metabolic disturbances. The classic signs and findings of this syndrome, central obesity, thin skin, osteoporosis, muscle wasting, and carbohydrate intolerance, are primarily manifestations of the catabolic effects of cortisol.

Obesity is the most common sign of hypercortisolism and is practically always present. In a recent review of 50 adults with Cushing's syndrome, 94 per cent exceeded their ideal body weight.[85] The obesity was generalized in 30 of the patients, and in only 20 was the typical truncal distribution of adipose tissue observed. Because of a concomitant loss of lean body mass, weight gain is usually not excessive, and it is uncommon to find patients with Cushing's syndrome weighing more than 200 lbs. The mechanism of the peculiar distribution of adipose tissue deposits in Cushing's syndrome is not understood. Subcutaneous adipose tissue deposits in the extremities are often diminished, and central redistribution occurs with particular enhancement of adipose tissue in the face, neck and supraclavicular areas which is so characteristic of the disorder. These effects cannot be attributed solely to the lipogenic effects of insulin, which result from the accompanying hyperinsulinemia, since insulin-mediated obesity is more commonly generalized[92] and most probably represent the result of the interaction of cortisol, insulin, and diet. One could speculate that cortisol may antagonize the lipogenic effects of insulin in some adipose tissue sites (i.e., those of the extremities) but not others, with the result that centrally located adipose tissue bears the brunt of excessive insulin secretion.

Body composition studies, though infrequent, provide the best information concerning the nutritional status of patients with hypercortisolism. There have been several studies of body composition in patients treated with corticosteroids, and in patients with hypercortisolism due to adrenal adenoma and bilateral adrenocortical hyperplasia. The administration of cortisol to human volunteers is associated with an increase in body fat.[19, 52] In patients with hypercortisolism due to adrenal disease partial body compositional measurements indicate a marked increase in body fat. In one series in which the data was available, fat represented 56 per cent (range 46 to 70 per cent) of the total body weight, in contrast to 25 to 35 per cent in normal subjects.[85] However, the fact that the actual weight of patients with hypercortisolism in another series was only 2 to 25 per cent above ideal body weight[26] indicates that the increase in weight due to adipose tissue is partially nullified by the decrease incurred in body protein.

In addition to obesity, reduction of body protein stores and lean body mass are clearly manifested clinically in severe cases of hypercortisolism by thin skin and striae, muscular wasting, and osteoporosis. Caliper measurements of changes that occur in the thickness of skin on the dorsum of the hand document the clinical impression of thin skin. In a series of 12 patients with hypercortisolism, mean skin thickness was less than normal, and in five patients it was below the normal range.[109] As would be predicted, derived compositional measurements which re-

flect body protein stores, such as the "body cell mass," are significantly altered by hypercortisolism. K_e was decreased in patients with Cushing's syndrome, whether expressed in absolute terms or on the basis of body weight.[26] The mean K_e/body weight ratio calculated by us from the data of two investigators for 17 patients[26, 85] is 31 mEq. per kg., a value significantly less than the normal range[67] of 35 to 40 mEq. per kg. and indicative of decreased lean body tissue. Lean body mass (body weight minus fat) in one series represented only 44 per cent (range 31 to 54 per cent) of the total body weight, in contrast to 65 to 75 per cent in normals.[85]

Further insight into the body compositional alterations that accompany Cushing's syndrome can be obtained from changes that follow therapy. After treatment of Cushing's syndrome, muscular atrophy disappears and body weight decreases. In a series of 12 patients studied after adrenalectomy, body weight decreased by a mean of 5.7 kg.[26] This loss was associated with a decrease of 6.1 kg. in body fat, and a concomitant increase in exchangeable body potassium of 300 mEq. and in "body cell mass" of 2.6 kg. Use of the formula: $\Delta \text{ protein} = \frac{6.25}{3} \times \Delta K_e$ reveals that dry body protein stores increased by 0.64 kg. Those patients demonstrating the greatest increase in K_e and cell mass following therapy were those who had the most severe muscular atrophy. Thus the changes induced in body composition by hypercortisolism are reversed with treatment with the single exception that osteoporosis remains unrepaired.[26]

Studies of nitrogen metabolism indicate that patients with Cushing's syndrome are generally in nitrogen balance, despite clinical evidence of wasting, if they are maintained on a diet containing 1 gram of protein per kilogram of body weight.[15] Ingestion of a diet high in protein, whether it contains adequate calories or not, results in positive nitrogen balance, while ingestion of a low protein diet is associated with negative nitrogen balance, regardless of the caloric content.[15] Administration of cortisone in doses of 200 mg. but not 100 mg. daily to patients with rheumatoid arthritis results in negative nitrogen balance.[95] Since rates of cortisol secretion are generally less than 100 mg. daily in Cushing's disease, the above changes in nitrogen balance undoubtedly represent the response to supraphysiologic doses of glucocorticoids. Results of studies of urinary ^{15}N excretion after the administration of ^{15}N-glycine to patients with Cushing's syndrome are helpful in understanding the changes produced in nitrogen metabolism by excessive glucocorticoids. ^{15}N excretion increases when normal subjects are fed a high protein diet and decreases when fed a low protein diet.[15] In contrast ^{15}N excretion in Cushing's syndrome is greater than normal,[70] but is unchanged by the protein content of the diet,[15] indicating that ingested amino acids are being degraded at a fixed and accelerated rate. The increased rate of ^{15}N excretion, while in nitrogen balance, suggests that protein synthesis was decreased and degradation of ingested amino acids was increased in Cushing's syndrome and supports the concept that cortisol exerts an antianabolic effect.[2] These types of studies also indicate that diet may be

an important factor in influencing body compositional changes in patients with Cushing's syndrome. Ingestion of a diet containing adequate calories and protein in the presence of excess cortisol results in the deposition of fat with minimal protein depletion.[53] If calories and dietary protein are restricted, as often happens as a result of concern on the part of the patient because of a change in appearance, then there is extensive protein depletion and osteoporosis.[95] These conclusions are consistent with the findings of fixed and accelerated amino acid degradation[70] and suggest that the body compositional changes in Cushing's syndrome can be minimized by ingestion of a diet high in protein. An extreme example of the marked protein depletion that accompanies hypercortisolism and poor dietary intake occurs in the ectopic ACTH syndrome. In this situation, the anorexia which frequently occurs as a result of the malignancy markedly diminishes dietary intake and allows maximum expression of the antianabolic effects of cortisol. The administration of testosterone to patients with Cushing's syndrome induces positive nitrogen balance,[2] improves skin thickness and strength,[2] and reduces ^{15}N excretion towards normal.[15]

In addition to their effects on body composition, glucocorticoids can also alter the growth pattern of children. Growth retardation is a common finding in children with Cushing's syndrome and in those treated with large and prolonged doses of glucocorticoids.[8, 108] It was initially suggested that this effect was mediated by cortisol suppression of growth hormone secretion.[31] Recent studies, however, have revealed that the release of growth hormone in response to hypoglycemia and arginine is normal in children treated with glucocorticoids and that growth retardation is probably due to glucocorticoid antagonism of the metabolic effects of growth hormone.[68, 83]

Diabetes mellitus or abnormal glucose tolerance can be observed in 80 per cent of patients with hypercortisolism. As a result of increased gluconeogenesis[104] and the production of insulin resistance,[71] hyperinsulinemia is a common concomitant of glucocorticoid excess,[71] and, as mentioned, may in some way be responsible for redistribution of body fat.

Glucocorticoid Deficiency

Although multiple hormonal abnormalities exist in Addison's disease, nutritional alterations are primarily the result of glucocorticoid deficiency. The findings of weight loss, increased insulin sensitivity, and susceptibility to spontaneous hypoglycemia are merely opposite to those findings observed with hypercortisolism. Weight loss is the predominant finding in Addison's disease, and the diagnosis can hardly be made in its absence. The loss of weight is multifactorial and can be ascribed to at least three mechanisms. Obviously, mineralocorticoid deficiency and the accompanying dehydration accounts for part of the decrease in weight. However, the most important factor probably is simply decreased caloric intake resulting from the accompanying anorexia, nausea, and vomiting. It has been suggested that glucocorticoids have a specific stimulatory effect on the "appetite center." Results of studies in animals also suggest

that malabsorption and steatorrhea may contribute to the weight loss in some patients with adrenocortical insufficiency.[82]

There is neither sufficient metabolic data nor studies of body composition from which objective conclusions can be reached concerning the nutritional status of patients with adrenal insufficiency. It might be assumed, as a result of the body compositional studies performed in Cushing's syndrome, that diametrically opposed changes would occur in adrenal insufficiency, that is, preservation of lean body mass at the expense of adipose tissue. However, it is important to disassociate those changes in nutrition that are due specifically to the metabolic abnormalities produced by a deficiency of cortisol from those due to alterations in the intake and absorption of food. Metabolic balance studies in patients with adrenal insufficiency have been complicated by the frequent occurrence of anorexia and nausea, which makes it virtually impossible to maintain a constant diet. There can be no doubt that the patient with adrenal insufficiency and weight loss is or has been in negative caloric and nitrogen balance and that the content of both fat and protein in the body are reduced. The questions arise however, as to whether the reductions that occur in fat and protein content are in the same proportion as those which occur in normal subjects in whom food intake has been curtailed, and whether any changes would occur at all in patients with untreated adrenal insufficiency if their intake of food and other nutrients were maintained.

Nitrogen balance in untreated patients with adrenal insufficiency is primarily a function of appetite and body weight.[35] Those patients whose weight is constant or increasing are in nitrogen equilibrium or in positive balance, while those whose weight is falling are in negative nitrogen balance. The administration of adrenal cortical extract is associated with increased appetite, weight gain, and nitrogen retention. We have unfortunately been unable to find any studies in which patients with adrenal insufficiency have been maintained on a constant diet prior to and while on therapy with glucocorticoids. The excretion of nitrogen in the urine of patients with adrenal insufficiency following therapy with dehydrocorticosterone, cortisone, or cortisol is uniformly increased.[101–103] However, such observations provide no insight into the changes which occur in nitrogen metabolism with therapy, because the intake of dietary protein was not kept constant and nitrogen balance data was not presented. As has been shown in other studies, the improvement that occurs in appetite, and secondarily in the intake of food, is associated with increased nitrogen excretion but positive nitrogen balance.[35] Glucocorticoids appear to be able to influence the partition and economy of fuel acutely in humans as demonstrated by the decrease that occurs in the respiratory quotient.[102] Such changes indicate that the proportion of calories derived from fat and protein are increased by glucocorticoids, while the proportion derived from carbohydrate is decreased. The restoration of mineral balance in patients with adrenal insufficiency with mineralocorticoids has been well documented[103] and is not the purpose of this discussion.

Important insight into the nutritional disturbances that occur in humans with adrenal insufficiency may be obtained from studies of fat and protein metabolism and body composition in adrenalectomized laboratory animals.[9, 14, 23, 47, 58, 99, 106, 107] The formation of urea and excretion of nitrogen in the urine is decreased by adrenalectomy in the rat,[9, 58] suggesting that adrenal insufficiency retards protein metabolism. However, weight gain does not ensue in adrenalectomized animals, because of associated changes in appetite and decreased food intake.[99, 107] As shown in studies of Cushing's syndrome in humans, as discussed earlier, diet is also an important determinant of changes which occur in body composition in adrenal insufficiency in animals and probably man. In force-fed rats, adrenalectomy has no influence on body composition, that is, there is no significant difference in the body fat and protein content of force-fed adrenalectomized rats when compared with normal rats.[99] In contrast, significant differences in body composition develop when ad-lib adrenalectomized rats are compared with normal rats. Protein constitutes a greater proportion and fat a smaller proportion of the body weight of adrenalectomized rats than of normal rats who ingest an identical quantity of calories.[99] Thus, adrenal insufficiency retards the mobilization of protein from the body during starvation, as well as the rate of weight loss.[106] The alteration in nitrogen mobilization that occurs in the absence of glucocorticoids is emphasized by the failure of nitrogen excretion to increase in response to stress in rats.[17] Increased excretion of nitrogen and ^{15}N in the urine after treatment of adrenalectomized rats with cortisone acetate has led to the suggestion that protein synthesis is probably increased in adrenal insufficiency.[14, 42]

As a result of the studies in humans and in animals, the following conclusions concerning nutrition in adrenal insufficiency seem justified. Impairment of protein mobilization, gluconeogenesis, and glycogen synthesis predisposes the patient with adrenal insufficiency to hypoglycemia when he is subjected to fasting. Maintenance of an adequate caloric intake prevents hypoglycemia and results in minimal nutritional alterations, as manifested by changes in body composition. Ingestion of an inadequate diet results in wasting, with a relatively greater loss in body fat than protein when compared to the normal response to starvation. Most of the non-mineral nutritional disturbances in adrenal insufficiency may be primarily a result of changes in appetite and food consumption rather than specific metabolic abnormalities due to the lack of cortisol.

Pheochromocytoma

Pheochromocytomas usually secrete a combination of epinephrine and norepinephrine on either a continuous or intermittent basis—an important point in understanding the symptomatology. Although patients with pheochromocytoma have many interesting signs and symptoms, the most important nutritional disturbances are weight loss and carbohydrate intolerance. Most patients with pheochromocytoma demonstrate varying degrees of weight loss. Although it is commonly stated that the presence of obesity excludes the diagnosis of pheochromocy-

toma, a recent study indicates that a significant number of patients may actually be obese. In a series of 22 patients with pheochromocytoma, eight patients exceeded their ideal weight; four of these were grossly obese.[57] It has been postulated that the secretory activity of the tumor is the major determinant of weight loss.[57] Nutrition is usually not significantly affected if secretion is intermittent, whereas continuous secretion produces hypermetabolism and weight loss. In only one of these obese patients was there sustained hypertension and presumably continuous secretion of catecholamines.

Studies of patients with pheochromocytoma have primarily emphasized diagnosis and therapy, and only recently have the metabolic abnormalities been more fully characterized. Unfortunately, to our knowledge there are no body composition studies in patients with pheochromocytoma. Therefore, the nature of many of the changes must be inferred from the effects of catecholamines on metabolic processes. Weight loss can be explained by the effects of the catecholamines on fat and carbohydrate metabolism, and their ability to produce hypermetabolism. Epinephrine and norepinephrine are potent lipolytic agents which when administered produce a prompt rise in plasma free fatty acids (FFA).[98] The elevated FFA that are often observed in patients with pheochromocytoma[24, 74] are derived from triglyceride stored in adipose tissue, and their mobilization results from activation of a specific "hormone-sensitive" cellular lipase.[98] The resultant increase in fatty acid oxidation may account for the calorigenic action of epinephrine and norepinephrine and the accompanying hypermetabolism. In contrast to the finding in hyperthyroidism, blockade of the catecholamine-induced FFA rise by prior administration of nicotinic acid inhibits most but not all of the calorigenic activity of the amine.[20]

The alterations of carbohydrate metabolism which occur in patients with pheochromocytoma are undoubtedly multifactorial in origin. Blood glucose and lactate concentrations are elevated in patients with pheochromocytoma as a result of the stimulation of glycogenolysis in liver and muscle by catecholamines.[41] Gluconeogenesis may also be stimulated by catecholamines,[28] and the increased availability of lactate from glycogenolysis in muscle and glycerol from hydrolysis of triglycerides in adipose tissue may provide the necessary substrate. Decreased peripheral uptake of glucose due to the effects of catecholamines on muscle[41] may also contribute to the hyperglycemia. However, the metabolic factors which increase the availability of glucose are accentuated by catecholamine-induced inhibition of insulin release.[74] The most important mechanism by which catecholamines produce carbohydrate intolerance probably relates to their effects on glycogen mobilization and insulin secretion. The effects of catecholamines on protein metabolism have not been clearly defined. The incorporation of amino acids into muscle in vitro is inhibited by catecholamines,[37] which, if operative in patients with pheochromocytoma, would promote protein wasting. Furthermore, the amino acids would also be available as gluconeogenic substrates.

In summary, excessive secretion of epinephrine and norepinephrine

produces weight loss through fat mobilization and hypermetabolism, and causes hyperglycemia by increasing glucose availability and decreasing insulin secretion.

EFFECT OF MALNUTRITION ON ENDOCRINE FUNCTION

It has become readily apparent in recent years that the normal release and secretion of many polypeptide hormones is regulated by the plasma concentrations of a number of specific nutrients. The control of glucagon, growth hormone, and insulin release by the concentrations of amino acids and glucose is well established but is beyond the scope of the present discussion. Suffice it to say that it is an exciting area which, in the future, will provide a much better understanding of the mechanism of metabolic control. We will limit our discussion to endocrine abnormalities resulting from impaired nutrition.

Although there are many similarities in the clinical manifestations of advanced malnutrition and hypopituitarism, there are clinical differences which should readily allow their differentiation. Contrary to traditional concepts, cachexia is seldom observed in patients with hypopituitarism,[91] and marked inanition should suggest the diagnosis of anorexia nervosa or severe neglect. In anorexia nervosa, in contrast to hypopituitarism, skin pigmentation is normal or increased, axillary and pubic hair is preserved, breast atrophy may not be striking despite wasting and amenorrhea, muscular strength is fairly well preserved, there is a high level of mental acuity and spontaneous physical activity, and there is often obvious concomitant psychopathology.[49]

Despite the suggestion of diffuse endocrine dysfunction in malnutrition, the only documented alteration involves the reproductive system. Genital atrophy and amenorrhea are frequently observed during famine and war and are also common concomitants of self-imposed starvation.[49] Urinary gonadotropins, measured by bioassay, are commonly absent or very low in patients with anorexia nervosa.[74] Low urinary estrogens and decreased estrogenic activity in vaginal cytologic studies are additional indices of hypogonadism in females.[22, 87] It has been stated that the synthesis and release of pituitary hormones is exquisitely sensitive to protein deficiency, and the decreased gonadotropins are a result of the malnutrition. However, as indicated below, there is no evidence that malnutrition decreases the synthesis or release of other pituitary hormones. Furthermore, the importance of psychic factors is emphasized by the fact that amenorrhea commonly precedes any major weight loss.[49]

Urinary 17-OHCS and 17-KS may be normal or low in patients with anorexia nervosa.[22] Normal pituitary-adrenal function is indicated by normal urinary 17-OHCS responses to metopirone,[62] and normal or elevated plasma cortisol concentrations with intact hypoglycemic responsiveness.[36, 55] Furthermore, in patients with anorexia nervosa, as well as patients with protein-calorie malnutrition, fasting plasma growth hormone concentrations are normal or elevated, and those which are normal respond in a normal fashion to insulin hypoglycemia.[36, 55] The

decreased thyroidal radioactive iodine uptake seen in anorexia nervosa[22] could reflect a functional impairment in pituitary TSH synthesis and release, but to this date has not been investigated. The resulting decrease in thyroid hormone synthesis that would ensue could be responsible for the reduction in oxygen consumption and the low basal metabolic rate commonly observed in famine and in this disorder.

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Infectious Disease in the Malnourished

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Medicine has long recognized that a host deficiency in nutritional state enhances the risk of an acquired infection; and when infectious disease follows, both course and severity often are heightened. A less appreciated circumstance is that infection, in turn, commonly intensifies the existing nutritional state so prominent in its origin. The two processes interact with one another.

An impressive mass of evidence from animal experiments demonstrates a varied response to combinations of the two diseases. The usual consequence is an increased clinical reaction as judged by death, complications, and duration, an effect beyond the summed result expected from either disease acting alone. This is synergism; the infectious process is exaggerated and a moderate nutritional disorder, such as weight loss due to protein-calorie malnutrition, is precipitated into manifest kwashiorkor. In some severe specific deficiencies in experimental animals the observed result is antagonism, the dietary effect being on the infectious agent rather than on the host. The resulting pathologic process is then less severe than usual. This has never been demonstrated in man since naturally occurring deficiencies are not ordinarily of the type required, and since it is unethical to induce them experimentally.

Investigations of the recent past have evaluated the significance of these experimental interactions in their relation to clinical medicine. More importantly, they have permitted recognition of a set of principles governing the behavior of individual nutritional disorders and the more common infectious diseases, as they occur together.[9]

In most industrialized nations the clinical and public health possibilities of an interacting malnutrition and acute infection are underrated, for the principal reason that the nutritional state of the general community is at a high level and infections occur far less frequently

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than formerly. Regions are identifiable, however, where the incidence of both conditions rivals that of earlier times, even matching situations presently characterizing most developing countries. Patchy distributions, small numbers in relation to total population, and a restriction to persons of lower economic status require the epidemiologic measurements of time, place, and person for detection. There is now a resurging national concern that such areas are more common and more extensive than previously appreciated. Yet they must be searched for. They are not the all-pervading circumstance so distinctive in developing countries.

In countries of the western world, an accompanying and striking decline during the past two decades in the incidence of most communicable diseases, and in deaths from that cause, has resulted in minimal opportunity for combined action of the two disease entities. The pronounced nutritional deficiencies so often employed to demonstrate synergism or antagonism under laboratory conditions, furthermore, are not those ordinarily seen in clinical practice. What is too little recognized is that nutritional deficiency disease in less developed parts of the world is of another order—far more frequent and more severe. Infectious diseases prevail there as they did 50 years ago in presently more privileged regions. That the practical problem of an interacting nutrition and infection is so far distant makes it no less tangible; and importantly, it involves three-fourths of the world population.

PATTERNS OF INTERACTION

The practical gain to clinical medicine and the public health extends beyond a clearer demonstration of interaction between malnutrition and infectious disease. That was established by multiple historical events of associated famine and pestilence. The situation was clearly evident in the early history of presently industrialized countries where the two conditions presented with equal intensity for so many years. Death rates were beyond present comprehension.

General biologic laws govern these interactions. In experimental animals some infectious agents regularly result in synergism with some nutrient deficiencies; others more commonly evidence antagonism, if any effect is observed. Still other experimental combinations show variable results: sometimes synergism, occasionally antagonism, but invariably dependent on recognizable and specific ecologic circumstances.

The broad generalization is that free-living infectious agents acting extracellularly lead with most nutritional deficiencies to synergism, while those confined to an intracellular existence frequently result in antagonism.

Whatever the infectious agent, the ultimate determinant is whether obligate dependence for successful invasion is on the enzyme system and metabolites of host cells or on the dietary requirements of the infectious agent. From this it follows that synergism is almost always the expected result when invasion by bacteria, rickettsiae, and intestinal

helminths or protozoa combines with malnutrition. Viral agents in similar combination, and systemic helminthic and protozoal invaders result variously in synergism or antagonism.

The effect of individual nutrient deficiencies on intercurrent infection can also be predicted to a considerable degree. General inanition is regularly synergistic, although occasionally antagonistic when the infection is systemic by a virus, protozoan or helminth. With few exceptions, protein lack is synergistic and usually strongly so. Avitaminosis A is regularly synergistic, with important after-effects occurring in many parts of the world. Vitamin D deficiency, by contrast, seldom has a determinable effect on infections, although with a few the result is synergism. The vitamin B complex and some individual B vitamins behave variably, being sometimes synergistic and in other circumstances antagonistic. Vitamin C deficiency is usually synergistic although antagonism has been observed. Mineral deficiencies take either course, largely according to the kind of infectious disease, and the extent of the underlying nutrient deficit.

MECHANISMS OF INTERACTION

A concept of synergism between a nutritional and an infectious disease requires a mutual contribution by each element to the resultant enlarged effect. The evidence is thus from two viewpoints: first, the means by which malnutrition favors infection; and conversely, the mechanisms by which infection magnifies an existing malnutrition.

The following summaries are drawn from the monograph *Interactions of Nutrition and Infection*,[9] in which a variety of observations from laboratory, clinic, and field fully document the frequency with which severity and outcome of infection are worsened by malnutrition. Prevalence also is increased for such common conditions as acute enteritis, upper and lower respiratory tract infections, and a wide range of others. Furthermore, in developing countries the high infant and preschool morbidity attributed to infectious disease is not characteristic of well nourished children of those areas.

Effect of Malnutrition on Infection

The relative importance of various potentially protective mechanisms whereby nutritional deficiencies influence resistance to infectious disease under natural conditions is indeterminate. They include the following.

Antibody Formation. Although other mechanisms may be equally important in defense against infection, the formation of specific antibodies for infectious agents or their toxins has received the most attention, perhaps because excellent techniques exist for detecting antibodies.

Severe deficiencies of protein, vitamin A, ascorbic acid, riboflavin, thiamine, pantothenic acid, biotin, and niacin-tryptophan are known to interfere with antibody production in experimental animals. A number of studies confirm that protein deficiency in man can limit the formation

of antibodies in response to an antigenic stimulus. Several reports show false-negative tuberculin reactions in malnourished patients with clinical tuberculosis. In human volunteers, antibody formation has been suppressed by inducing metabolic deficiencies of pantothenic acid or pyridoxine by feeding the corresponding antimetabolites, desoxypyridoxine and omega methyl pyridoxine. A similar effect has been observed in severe pellagra and with a moderately severe deficiency of several of the B vitamins.

PHAGOCYTIC ACTIVITY. The microphages, and the macrophages of the reticuloendothelial system, have an important part in protection against infectious diseases, particularly those caused by bacteria. Nutritional deficiency can reduce both the number and the phagocytic capacity of these cells. Children with kwashiorkor have little or no leukocyte response to superimposed infections. Macrophage activity is decreased in the presence of deficiencies of vitamin A, ascorbic acid, thiamine, and riboflavin in experimental animals. Both animal studies and clinical observations of folic acid deficiency have shown production of phagocytes in mammalian bone marrow to be depressed to the extent of nullifying the effect of protective antibodies.

TISSUE INTEGRITY. Except as an aftermath of protective immunization, antibody formation takes place only after the infectious agent has entered the host. Its action then is to minimize possible pathological consequences of infection rather than to act as a preventive. The same is true of phagocytosis. The integrity of the skin, mucous membranes, and other epithelial tissues does serve a protective capacity through preventing entry of an infectious agent. The various pathological changes which occur in tissues depend on the type and severity of the nutritional deficiency. Mucus secretions may be reduced or absent, mucosal surfaces become easily permeable, and changes take place in intercellular substance; there may be epithelial metaplasia, edema in underlying tissues, and accumulation of cellular debris to form a favorable culture medium for the infectious agent. Deficiencies in vitamin A, ascorbic acid, niacin, and protein are especially likely to cause tissue changes that lower resistance.

WOUND HEALING AND COLLAGEN FORMATION. How long an infection will be disabling depends on how rapidly it can be localized and contained. Nutritional deficiencies affect not only tissue integrity but also wound healing, fibroblastic response to trauma, walling off of abscesses and collagen formation. In protein-deficient rats, the walls of induced sterile subcutaneous abcesses were much thinner than those of spontaneous or induced abscesses in well nourished animals. The fibroblastic response in deficient rats is markedly reduced, and as a result fatal septicemia frequently follows:

Protein deficiency, especially with an inadequate intake of methionine, interferes with conversion of procollagen to collagen and weakens the tensile strength of collagen fibers. Ascorbic acid must be adequate for synthesis of the amino acids from which collagen is formed, particularly hydroxyproline and hydrolysine, which are almost unique to collagen. The skin at the edges of wounds in scorbutic guinea pigs shows

almost no hydroxyproline. Restoration of ascorbic acid to the diet induces rapid production of hydroxyproline, and wound healing.

Nonspecific Resistance Factors. The importance of various nonspecific mechanisms of resistance is difficult to assess. The effect of nutritional deficiencies on most of them is not clearly understood. The so-called lysozymes, which help to destroy pathogenic microorganisms, are found in tears, sweat, saliva, and other body fluids. Their activity apparently is reduced by generalized malnutrition, particularly by vitamin A deficiency.

Properdin is a euglobulin present in the serum of all normal animals thus far tested; it is associated with natural resistance to many diseases of bacterial, viral, and even protozoal origin. The properdin system is vulnerable to nutritional deficiency in formation of the compound itself, as well as in the presence of an appropriate complement of magnesium. The only published evidence, however, is a report of marked reduction of properdin in the serum of pantothenic acid-deficient rats.

Interferon is a natural product of animal cells that supplements other mechanisms of resistance to viral and some other infections. It appears to act by uncoupling oxidation from phosphorylation, so that the production of adenosine triphosphate is inadequate for replication of the infectious agent. Since interferon is a protein molecule, it seems likely that its formation is depressed in deficiency states in which protein synthesis is impaired.

Most of the destruction of bacterial toxins or resistance to them in animal hosts occurs as the result of combination with specific antibodies. There is some evidence of other mechanisms also. For example, rats suffering from deficiencies of B vitamins or vitamin A are more susceptible than controls to diphtheria toxin, despite similar antitoxin titers and rates of disappearance of injected toxin in the two groups. There are no clinical observations in man.

Changes in the intestinal microbiota (particularly the bacterial flora) induced by diet can influence susceptibility to some intestinal pathogens. In kwashiorkor, bacteria of the lower intestinal tract tend to appear at higher levels. In milder degrees of protein malnutrition, it seems likely that intestinal organisms not normally pathogenic to the well nourished host may cause diarrheal disease. The frequency and severity of such episodes are decreased by dietary supplements. Changes in gastrointestinal mobility secondary to malnutrition may also affect the severity of protozoal and helminthic infections.

Endocrine factors are intimately involved in a number of the mechanisms of resistance already mentioned. Examples include the loss of resistance to infection in adrenalectomized animals and patients with Addison's disease, and the serious problem of secondary infections in poorly controlled diabetic patients. Prolonged adrenocorticotrophic hormone (ACTH) or cortisone therapy, however, increases the spread of many infections, presumably because these hormones inhibit local inflammatory reactions at the site of bacterial proliferation. These observations bear on the question of how malnutrition influences resistance to infection, since protein deficiency, caloric deprivation, and a number of other nutritional deficiencies influence endocrine balance.

Effect of Infection on Nutritional Status

One of the earliest and most constant consequences of infection is loss of appetite and a decreased tolerance for ingested food. Another is the almost universal tendency to change the diet of patients to one more liquid and higher in carbohydrates, at the expense of foods that are good sources of protein and other essential nutrients. The practice is especially common in the feeding of young children in less developed areas. Often when a child has diarrheal disease or other acute infection, milk and solid foods are eliminated in favor of starchy gruels and cooking water from cereal grains or plant leaves. Therapeutic agents such as purgatives may reduce intestinal absorption, or in the case of sulfonamides and antibiotics, interfere with intestinal synthesis of some nutrients. The direct influence of fever in increasing both basal metabolism and loss of nutrients in sweat must also be taken into account.

PROTEIN. Acute infections cause a response qualitatively the same as that observed in states of pain, anxiety, fear, and other psychological stress. Mediated by cortisone and insulin, the stress reaction mobilizes amino acids from skeletal muscle and other tissues from which they can be spared, for gluconeogenesis in the liver. This necessarily depletes body protein because the amino acids thus mobilized are deaminated to provide the carbons of glucose, and the nitrogen is excreted in the urine largely as urea.

Nitrogen losses during severe infectious diseases of bacterial origin—typhoid fever, tuberculosis, and many others—have long been recognized and can be equivalent during the acute phase of the illness to the nitrogen of 2 to 3 kg. of muscle. Rickettsial and viral diseases have the same capacity. Respiratory infections, tonsillitis, otitis media, staphylococcal abscesses, and even immunization against smallpox and yellow fever induce the stress reaction with consequent increased urinary nitrogen loss.

A stress of short duration may be balanced by an increase in nitrogen retention during the same or succeeding 24 hours. However, the catabolic period associated with an infectious disease episode is likely to last for several days, and the anabolic period of increased nitrogen retention is generally twice as long. After the acute stress is over, dietary amino acids are returned to the depleted tissues, and hence protein intakes above maintenance levels are required. In individuals already depleted by low levels of protein intake, the urinary loss of nitrogen during stress is less than that observed in well nourished persons. Nevertheless, increases in urinary nitrogen loss during minor infections have been found even in experimental subjects receiving a nitrogen-free diet.

With so many factors adversely affecting protein nutritional status during infectious disease, it is not surprising that in underdeveloped countries the protein deficiency disease, kwashiorkor, is commonly precipitated by acute diarrheal disease, measles, and other childhood infections in persons whose nutritional state is already precarious. Similarly, infections are responsible for much of the protein deficiency seen in adults, especially attacks of chronic nature.

Vitamins. Blood levels of vitamin A are reduced in acute infections, sufficiently that xerophthalmia and keratomalacia frequently follow in children receiving diets deficient in that nutrient. Giardiasis is known to interfere with vitamin A absorption, and any intestinal infection producing malabsorption will have the same effect.

Pneumonia and malaria have been recognized as significant factors in the occurrence of beri beri in civilian populations; dysentery was a common precipitant of that disease among Japanese prisoners of the Second World War.

Clinical manifestations of thiamine, folic acid, vitamin B_{12} and ascorbic acid deficiency have all been related to a preceding infection of a vulnerable host.

Minerals. Hookworm infection, if sufficiently severe, is well recognized as responsible for enough loss of blood to induce microcytic-hypochromic anemia even when dietary intakes of iron appear adequate.

Increased losses of calcium and phosphorus have been reported in tuberculosis of both man and guinea pigs. Losses of sodium, chloride, potassium, and phosphorus are of particular moment in diarrheal diseases of infectious origin, and an important cause of death.

Lipids. A marked increase in concentrations of total serum lipids has been observed in patients with gram-negative bacillary infections. Infectious or serum hepatitis causes heightened levels of serum triglycerides and cholesterol. Absorption of fat is decreased in infections that provoke diarrhea. Increases in liver fat and some degree of steatorrhea have been reported in patients with influenza and pneumonia, and are probably associated with other infections.

Anemia of Infection. Chronic infections of almost any type are likely to produce the so-called anemia of infection by shortening the life span of erythrocytes and interfering with red cell production in bone marrow.

WEANLING DIARRHEA

Experimental studies are useful but there is no substitute for clinical examples. Two of the commonest infectious diseases of man, weanling diarrhea and measles, illustrate the way in which nutritional deficiency and infection combine synergistically. Acute intestinal infection of infants and young children, with diarrhea the main presenting sign, is a minor occurrence in highly developed regions. This was not always so. Acute diarrheal disease has lost the significance it had no longer than 50 years ago, a time when frequency and mortality matched that now present in the remaining bulk of the world today. Many factors account for the change, including a more favorable economy, improved environmental sanitation, as well as gains in human nutrition, the control of communicable diseases, and the evolution of modern pediatrics.

Acute diarrheal disease is an outstanding feature of life in less developed regions—from the arctic to the tropics. Repeated attacks occur during and immediately after weaning. Malnutrition is especially

common at that time. The two conditions are so interrelated that the illness is appropriately termed weanling diarrhea.[2] Not only is the condition worldwide, it is unsurpassed as an illustration of synergistic interaction between malnutrition and infection: costly in the disability it causes, in the deaths that follow, and in immediate and long-term after-effects.

Infants in developing regions are almost universally breast-fed, the necessity being so great that "nurse or die" is a common axiom. They do well in growth and development during the first 3 or 4 months; gain in weight keeps pace with that of well nourished children in more favored parts of the world. The nutritional demands of rapid weight increment in those early months soon surpass the food supply provided by breast milk.

The infant's need for more food becomes serious usually by the fifth or sixth month. The ordinary food supplement does not provide nutritional requirements; by custom or economic necessity it consists of gruels or starchy foods that lack the required animal protein. Weight gain is depressed, depletion sometimes reaching extreme limits, with the result that departure from the weight curve characteristic of well nourished infants becomes clearly evident in the latter half of the infant year, more forcefully so in the second year, and often continuing through the third year as breast feeding and supplementation remain insufficient. With completed weaning, the ordinary family diet with some restrictions takes its place.

The frequency of diarrheal disease runs a parallel course. Attack rates are at low levels during the wholly breast-fed stage. Episodes become more frequent as supplementation follows; a greater incidence occurs with milk alone added; diarrhea is more frequent when solid foods are included; and the greatest frequency is in late weaning, with almost equivalent rates in the immediate three months thereafter.[4]

At this peak, rates average four attacks per year, with sometimes as many as eight or ten. The disease contrasts with the milder indisposition of the well nourished child of the western world. Onset is acute and rapidly progressive, with multiple daily stools varying from three to as many as 20. A variable proportion of patients, commonly a third, have blood or mucus in the stools, and frequently pus. Fever may be absent, but a low grade temperature rise is usual, along with malaise, toxemia, intestinal cramps, and tenesmus. The usual clinical course lasts four to five days. In malnourished children, a low grade indisposition often continues for a month or more, sometimes as long as 3 months, with irregularly recurring loose stools, short of true diarrhea, and a progressively depleted nutritional state. In some 15 per cent of cases, this takes an exaggerated form, with recurrent episodes of acute diarrhea interspersed with periods of freedom, and recognized as chronic recurrent diarrheal disease. Dehydration and electrolyte imbalance are common and difficult to control.

The above usually coincides with an increasing degree of malnutrition. Weight gain turns upward after weaning, so that in the years immediately thereafter it parallels that of well nourished children,

although at a lower level, and the frequency of diarrheal disease declines remarkably.

High incidence of diarrheal disease is not a matter of age. In a given locality, it lessens when weaning is completed early; it continues high or at even greater levels with long-delayed weaning. In countries such as Trinidad where custom dictates completed weaning early in life, peak prevalence of diarrheal disease also is in the early months; when it is long delayed as in Guatemala (mode 25.4 months) the peak is late in the second or early in the third year.

In a particular region, for all preschool ages and according to extent of impaired nutritional state, diarrheal attacks increase in straight-line progression from low rates accompanying a normal nutritional state (within 10 per cent of the standard for growth of well nourished children) to greater frequency with mild impairment (10 to 24 per cent deficiency in weight) and greater still with 25 to 39 per cent. When the deficiency in weight for age exceeds 40 per cent, rates are greatest. Severity of disease follows the same curve.

Disease-specific death rates for diarrheal disease were in accord with the frequency of depleted nutritional state. In the Punjab experience,[2] in which the mode for completed weaning was 19.4 months, deaths per 1000 live births per year were 20.6 in the first 6 months of life and 58.6 in the second six months; in the first half of the second year they were 34.8, and in the last half, 7.4 per 1000 population of that age per year. The broad situation is best illustrated by the Guatemalan field study[1] in which deaths from acute diarrheal disease were 25 times greater in the first year of life than for the same period in the United States; for children aged 1 through 4 years the death rate was 519 times that of children in the United States. For many countries, deaths among young children are so numerous that diarrheal disease becomes the first cause of death for all ages and total population.

MEASLES IN THE MALNOURISHED

Measles permits direct comparison of the clinical behavior of infectious disease in the malnourished and the well nourished, without the complicating differences in disease distributions from place to place and through multiple attacks. Everyone has measles and they have it once; the recently developed measles vaccines have yet to be sufficiently used on a world-wide basis to affect this relationship.

In rural Guatemala,[3] more than half of cases in a series of epidemics were among children less than 3 years old. In industrialized countries the common age of attack is 6 years, when school begins. The excessive fatality of measles in developing regions is well established; in the Guatemalan experience it was 6.8 per cent. The measles death rate for the country was 268 times that for the United States in a comparable period. Several investigations in developing areas have emphasized the capacity of measles to precipitate kwashiorkor in a protein-deficient child.

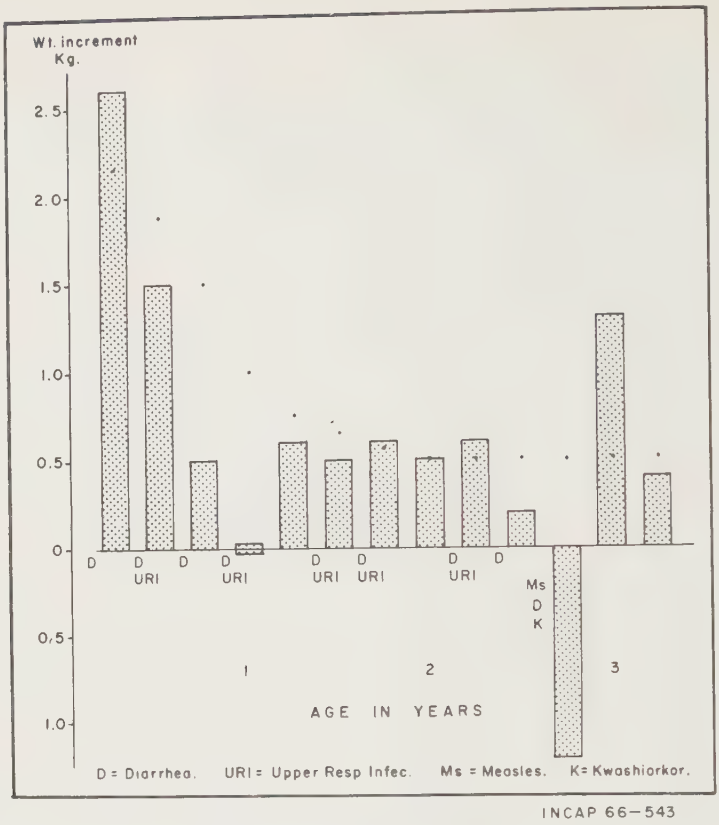

Figure 1. Quarterly increments of body weight in kilograms and preceding illnesses of a Guatemalan boy who at age 33 months contracted measles, a complicating diarrhea, and subsequent kwashiorkor. Dotted line denotes mean weight increments of well nourished children.[6]

A more virulent strain of measles virus is not the answer, because children of middle and upper class families of the same region have a wholly ordinary disease. The high fatality occurred at those ages when malnutrition prevails, during the weaning period. The following case history is from a Guatemalan village epidemic.[6]

A boy aged two years and nine months, the third child in an Indian family, had breast milk as the sole food during the first three months. Weaning started then with the addition of food supplements from the family table. Breast feeding ended in the 22nd month, the child subsisting thereafter on selected foods served by the family, predominantly corn (tortillas), vegetables and sometimes the broth of a meat and vegetable soup.

During the first year the child had the usual medical history of infants born in that environment: four attacks of acute diarrheal disease, totaling 37 days, and 23 days of upper respiratory disease in two episodes; in all, he had 60 days of illness, or the equivalent of 17 per cent of his first year, distributed by quarterly periods as shown in Figure 1.

The first and fourth quarters of the second year were free of illness, but 26 days of diarrheal disease and 25 days of respiratory infection were accumulated

during the second and third quarters, again 15 per cent of the second year, in four separate illnesses. The third year had provided a similar experience when measles developed at 33 months. The disease was associated with a severe diarrhea of 9 days' duration first evident in the prodomal period preceding the rash of measles. Kwashiorkor developed three weeks later.

The effect of this succession of illnesses on growth and development and the ultimate nutritional collapse precipitated by measles is illustrated by the quarterly variations in weight. Weight increments are taken as more expressive of weight change at a particular time than actual accrued weight.

The rate of growth in the first three months was better than the standard. Subsequently, in the face of ensuing infections, rates of growth decreased progressively until at the end of the first year there was no demonstrable increment. With no illness during the first 3 months of the second year, a normal growth pattern resumed and despite minor illnesses was maintained until the second quarter of the third year. A 12-day attack of diarrheal disease at that time decreased the weight increment by half. Shortly thereafter, the patient had measles and a second episode of diarrhea.[8] The result was an inversion of the growth pattern, a marked loss of weight and ultimately kwashiorkor. With hospitalization and a high protein diet, the weight rebound was gratifying.

Measles and a complicating diarrhea were clearly the precipitating cause of kwashiorkor. The real origin was more remote, primarily in the long series of acute infectious illnesses, to give a moderate protein-calorie malnutrition. Measles decided the issue.

Measles is no isolated instance among childhood infections. Whooping cough and chicken pox have an almost equal effect. That train of events is associated with all of the common communicable diseases of early childhood.

NUTRITIONAL ECOLOGY

That nutritional deficiency diseases tend to be chronic, and that most infectious diseases are acute, greatly simplifies questions of synergism and antagonism when these two conditions occur together. The nutritional disorder almost invariably precedes the infection. When two acute processes are so associated, for example diphtheria and scarlet fever, the order in which they appear influences the subsequent result importantly.

The regularity of an infection superimposed on a nutritional disorder leaves most of the significant variables to be found within the environment, to a lesser extent in the affected host. Nutritional ecology thus becomes the dominant consideration in their interaction. The time that association occurs and how long it lasts are key determinants of the end result.

Timing

Nutrient demands are greatest and malnutrition thus more likely during periods of rapid growth. The risk of infection is continuous, and

greater in less developed countries than elsewhere. The opportunity for synergistic interaction of nutrition and infection is therefore pronounced at recognized times of life.

Growth is greater in the first 3 months of life than in the remainder of the first year; greater in the second year than in other years of the preschool period, as the child takes on an independent existence with increased risk of disease and injury. It is greater in preschool years than during school ages. The curve extends back into fetal life, when rates of growth are highest.

By animal experiment and by observation of children dying accidentally, Winick[12] has advanced a concept that growth is in three stages. The early period is mainly through cell proliferation, but with proportional increase in organ weight and protein content. There is a second phase in which cell proliferation continues but at a slower rate than cell enlargement, usually from late fetal life and variously for different organs and tissues after birth. A third phase follows, wholly postnatal, in which growth is due entirely to increase in cell size. This separation of growth phases has important connotations. Inhibited cell proliferation appears irreversible, that of cell size remediable by proper feeding.

That infection can occur in fetal life when cell proliferation is most active is well demonstrated by maternal rubella during early pregnancy. That it occurs more generally is supported by recent studies of IgM in fetal serum. The significance of maternal infections during pregnancy and of the infant in the early years of life in the face of a coexistent malnutrition is manifest.[5] Weanling diarrhea and the other common infections of early childhood are thus of greater significance than when they occur later in life.

Timing of an interacting nutrition and infection again comes into play as nutritional state deteriorates under physiological stress, notably at puberty, in pregnancy, and during lactation. The increasing frequency of teenage pregnancies in the United States, and their common occurrence in populations of less developed regions, adds significance to this part of the problem. The prospective mother is called upon to sustain her own genetic potential for growth as well as meet the demands of a developing pregnancy. The difficulty is intimately connected with the fetal malnutrition already mentioned.

Risks of a synergistic interaction of nutrition and infection are further related to a variety of social influences, largely dependent on custom, habit and culture. They include elderly persons living alone, food faddists, persons on imbalanced reducing diets, teenagers with aberrant food habits, patients with chronic degenerative and metabolic diseases, and residents of institutions.

Duration of the Synergism

Duration of the antecedent nutritional deficiency, the length of time it is associated with an infection, and the extent of after-effects all enter into determining the significance of the interaction.[11] The closely spaced postnatal episodes illustrated in Figures 1 and 2 constitute an essentially chronic disease process, because of the brief interval between attacks

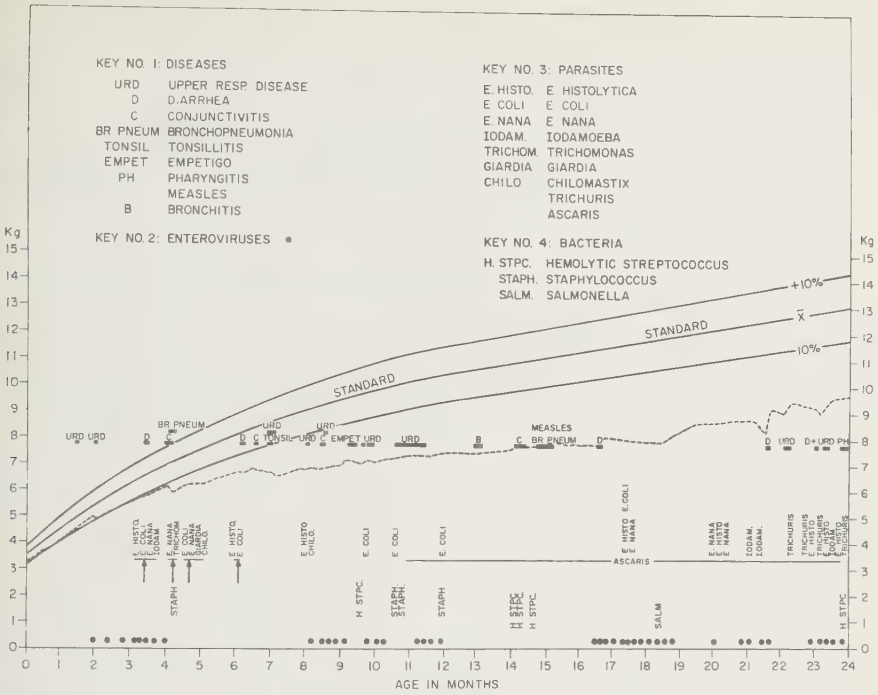

Figure 2. Recurring illnesses, invasion by bacteria, parasites, and enteroviruses, and ensuing malnutrition in a 2 year old Mayan village child, Guatemala. Adapted from Mata et al.[4]

and their great number.[7] The chronic recurrent diarrheal disease earlier mentioned is indeed such a continuing process. When the burden of infection is heavy during the critical phase of growth by cell proliferation, the effects are particularly serious.

Place

In less developed regions, it is reasonable to devote attention to a general population on a place basis, because malnutrition is so generally prevalent and infectious disease so universally existent. Assessment of the problem involves practically all children, and prevention and control are universally applicable.

To follow the same approach in developed countries is wasteful and minimally productive. To be sure, there are areas in which an associated malnutrition and infection is more significant and the need for control greater than in others. More benefit is promised by attention less to places than to kinds of people. In good and poor districts there are fractions of the population more affected than others. The groups most involved are those listed earlier. The indicated approach is more social than geographical, and should deal with the vulnerable segments of the population.

SIGNIFICANCE

In developing countries the synergism of malnutrition and infection is responsible for most of the excess mortality seen in young children. It contributes to greater mortality of older persons. It adds importantly to the morbidity that interferes with the schooling of children and the productivity of adults. Its occurrence in the young can contribute to subsequent impaired learning and behavior.

For these reasons a synergism of nutrition and infection has public health significance in industrialized countries in those pockets of poverty and underprivilege where poor nutrition and high grade environmental exposure to infection persist.

For the clinician, the possibility of synergism is always present wherever and whenever the two conditions coexist. The patient whose nutritional state is impaired by chronic disease, unwise dieting, food fads or any other cause has a greater probability of acquiring an infection. Clinical management of either nutritional deficiency or infectious disease thus necessarily takes into account the possibility of both and their potential interaction.

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Current Concepts on Trace Minerals
Clinical Considerations

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The development of improved methods of analysis and of animal husbandry have led to an increased understanding of the role of trace elements in metabolism. Appreciation of their importance in human nutrition is unfolding. While the roles of iron, iodine, fluorine, and cobalt (as vitamin B_{12}) in human nutrition are relatively well understood, information concerning human physiology of copper, zinc, chromium, selenium, manganese, molybdenum, and cadmium is less complete. Accordingly, this discussion will concern the latter elements. The reader is referred to Underwood[96] for a review of the metabolism of other trace elements whose metabolic functions are even more obscure.

Five of these elements (copper, zinc, chromium, selenium, and manganese) are clearly essential for mammals. They have specific metabolic functions, and deficiencies of them result in syndromes that have in some instances been observed in man. Examples are dwarfism and hypogonadism associated with zinc deficiency,[67, 75] and anemia due to copper deficiency.[13] Molybdenum is essential for fowl;[31] its requirement in mammalian metabolism is obscure. Cadmium, a toxic element having no known metabolic role, is included in this essay because of its possible role in hypertension.[81]

Similar factors affect the biological availability of certain of these

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essential elements.[51] Thus, chelating componds in the diet (phytic acid, phaeophytin, alkaline clays) may depress the absorption of zinc and copper in animals, and presumably in man. Interactions that affect absorption or metabolism occur between certain of these elements. For example, increased dietary levels of molybdenum in the presence of sufficient inorganic sulfate will decrease the absorption of copper in sheep,[96] while the combination of increased calcium and phytate in the diet will severely depress zinc absorption.[55] It remains for future research to clarify such trace mineral interrelationships in man.

Availability of trace elements for absorption is also affected by the intestinal milieu. For example, an acid pH seems to improve the availability of copper[20] and zinc.

Many of the metabolic functions of trace elements are similar.[96] In some instances they influence the conformational state of particular proteins or other molecules; in others they serve as coordinating forces between organic molecules. Some act as integral parts of enzymes (metalloenzymes) and are essential for the function of the enzymes. In this latter instance the metal is present in a constant amount, the reduction or removal of which inactivates the enzyme. Cobalt is an example of a trace element whose function in man is related to its position in a specific nutrient, the cyanocobalamin molecule (vitamin B_{12}). Iodine functions as the halide in thyroxin.

Some of the factors which determine the requirements of a given trace element and the effects of deficiency include: species, age, sex, metabolic state (e.g., pregnancy, growth, physical exercise), and environmental conditions. The effects of these influences in man are only beginning to be understood. In the following discussion, those aspects of both animal and human trace element nutrition which appear to be of either present or future clinical importance will be discussed.

The reader is referred to Tipton[94, 95] for tables summarizing the tissue content of trace elements.

COPPER

The discovery by Hart and associates[29] in 1928 of milk anemia in rats established that copper is essential for the utilization of iron in hemoglobin formation in higher animals. Since then, copper has been found to be a component of a variety of oxidative enzymes, including cytochrome oxidase, tyrosinase, ascorbate oxidase, and uricase. Copper deficiency in animals affects many systems, and may be manifest by anemia, hypopigmentation and abnormalities in texture of hair, impaired collagen and elastin formation with resultant effects on osseous connective tissue and defective structure of vascular walls, impaired reproduction, and failure of myelination. Since the early studies of Hart et al., copper metabolism has been studied in detail by many workers.[10] Perhaps those of Cartwright and Wintrobe[10] in swine have contributed the most knowledge that is seemingly applicable to man. A few clinical studies in infants with protein-calorie malnutrition are also of value in this regard.[13, 40, 46]

Copper Metabolism

Human adults contain approximately 80 mg. of copper. Concentrations in newborn infants are greater. Roughly 60 per cent is found in muscle, and 20 per cent is found in the liver. The highest concentrations are found in liver, heart, kidney, brain, the eye, and hair. Normal serum copper in adults is in the range of 90 to 150 micrograms per ml., of which 93 per cent is bound to ceruloplasmin and 7 per cent to albumin. Serum levels in women are usually higher than those in men. Copper attached to albumin is loosely bound and appears to be the fraction available to the tissues. Although serum concentrations of copper are affected by diet, disease, and hormones, they vary by less than 30 per cent in a given individual from day to day and week to week.[10] Pregnancy or exogenous female hormones cause ceruloplasmin, and therefore serum copper concentrations, to be increased. Of interest is the fact that newborn infants have lower serum concentrations of copper than their mothers, while their livers contain considerably higher concentrations of the cation. Presumably, the high content of copper in the liver provides a store of available cation during the period of nursing, milk being a poor source of copper.

Ceruloplasmin, the major serum component containing copper, is a metalloprotein which is synthesized in the liver. It is present in the α-2-globulin fraction of serum in two chromatographically different forms. It has a molecular weight of 151,000 and contains eight atoms of copper per molecule. The normal serum concentration of ceruloplasmin is 34 ± 4 mg. per 100 ml. In erythrocytes, which contain roughly 75 micrograms per 100 ml., copper is 60 per cent bound by a metalloprotein, erythrocuprin. Nonerythrocuprin copper is labile and is thought to be in equilibrium with the serum.[20] Erythrocuprin has a molecular weight of 35,000 and contains two atoms of copper per molecule. Its function is unknown. Frieden[25] has presented evidence that ceruloplasmin is a ferro-oxidase and may participate in the formation of Fe III-transferrin, the transport form of iron. He has suggested that the function of ceruloplasmin, therefore, is the mobilization of iron from stores such as the liver to the marrow, and thus the stimulation of hemoglobin biosynthesis. The precise mechanism of this phenomenon remains unknown.

Hypocupremia occurs in patients with nephrosis, Wilson's disease, and protein-calorie malnutrition, and in infants fed for long periods exclusively on milk.[13] In Wilson's disease the decrease in plasma copper reflects a decrease in both the ceruloplasmin and albumin bound copper; levels may be as low as 9 ± 5 mg. per 100 ml. In nephrosis, serum copper levels in the range of 40 micrograms per 100 ml. are not unusual.

Hypercupremia may reflect excessive intake, which may result from eating food prepared in copper cooking vessels, or which may be associated with several chronic or acute infections (leukemia, Hodgkins' disease, certain collagen disorders, some anemias, hemochromatosis, myocardial infarction, and hyperthyroidism).[96] In the United States, dietary copper intake is in the range of 2 to 5 mg. per day. Of this amount, 0.6 to 1.6 mg. are absorbed in the adult,[10] primarily in the stomach and proximal small intestine by an ill-defined mechanism.[20]

Copper from the intestine enters the serum and is loosely bound to albumin. It is thus transported to the tissues (90 per cent to the liver) where it is incorporated into a variety of metalloproteins and enzymes. The liver is the organ responsible for storage of copper, its incorporation into ceruloplasmin, and its excretion in the bile. Very little of the copper in bile appears to be reabsorbed. In contrast to bile, urine contains minute amounts of copper (20 micrograms per day). Urinary copper is increased in patients with cirrhosis of the liver or Wilson's disease. The latter individuals may excrete as much as 1500 micrograms per day. Small amounts of copper are excreted in sweat and lost with menstruation.

Copper is stored in liver, primarily in the parenchymal cells. Newborns have considerably more liver copper than adults. Diseases associated with increased concentrations of liver copper include Wilson's disease, polycythemia vera, hemochromatosis, cirrhosis, yellow atrophy of the liver, tuberculosis, cancer, and severe chronic disease with anemia.

The mechanisms controlling the passage of copper through the body are unknown. Dowdy[20] has presented a working scheme.

Copper Deficiency

Because copper is so widely distributed in food and cooking utensils, it seems improbable that copper deficiency occurs in man except under extreme conditions. Dietary sources of copper are similar to those of iron, the major exception being high levels of copper in shellfish and Crustacea. Other rich sources of copper are nuts, legumes, cocoa, and organ meats. Foods that are poor sources of copper include margarine, honey, white sugar, cheese, butter, and milk. Human milk contains 600 to 900 micrograms per liter early in lactation and 150 to 170 micrograms per liter during later months. Copper requirements of rapidly growing infants have been estimated to be in the range of 42 to 135 micrograms per kg. body weight.[59] It is thus easy to understand how a diet prepared exclusively from milk might, if given to an infant for many months, produce a deficiency in copper.

Copper deficiency has occurred in infants fed a milk diet for several months following their recovery from kwashiorkor.[13] Their serum copper levels ranged from 42 to 72 micrograms per 100 ml. (normal = 110), and they progressively developed a hypochromic microcytic anemia that was responsive to copper but not to other hematemic agents (Fig. 1). The two patients reported radiographic changes of the bone similar to those described in copper-deficient puppies, and one experienced a pathologic fracture. In addition to the anemia and brittle bones, they exhibited leukopenia which also was copper-responsive.

Infants with untreated protein-caloric malnutrition have also been found to have low serum copper concentrations. The complexities of their illnesses have made interpretation of these observations difficult.[40, 46, 77]

Copper deficiency has been studied in more detail in animals. In swine,[10] a hypochromic microcytic anemia occurs with a decrease in

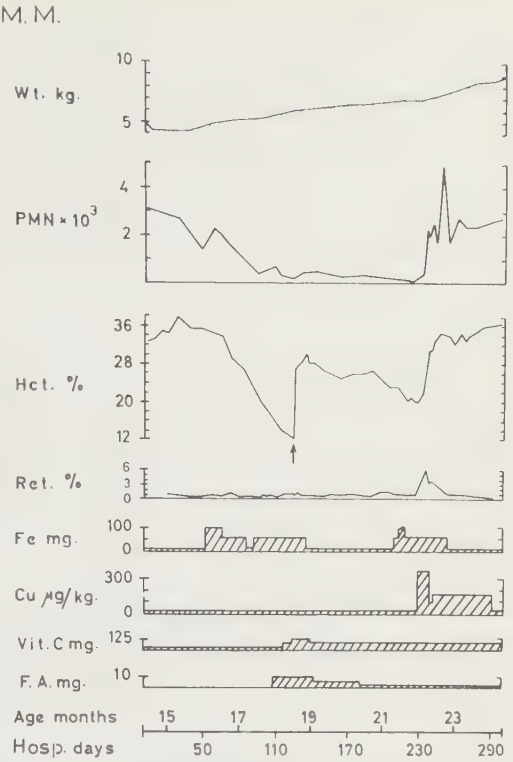

Figure 1. Copper-responsive anemia in an infant. Although weight increased throughout the period of observation, the hematocrit decreased to the level where a transfusion was required (indicated by the arrow). The leukocyte count also decreased to low levels. Reticulocytosis and an increase in hematocrit occurred in response to copper administration, and not following administration of iron, ascorbic acid, or folic acid.[13]

hematocrit of 30 per cent in 100 days. Iron absorption is impaired and tissue concentrations of iron are low. Parenteral iron will not improve hematopoiesis. Since it does not appear that copper is essential for the function of any enzyme in the heme pathway,[42] it has been suggested that its role is an undefined one, involving iron absorption and iron release from tissues such as the liver[47] for subsequent utilization by the marrow.

Copper-deficient sheep demonstrate loss of hair color and of curl. The former abnormality probably occurs because copper is a constitutive part of tyrosinase, the enzyme essential for the synthesis of melanin from tyrosine. The changes in hair texture may be due to abnormal formation of cross links between the protein strands of the hair. Copper-deficient wool has increased numbers of thiol groups and fewer dithiol groups than normal. It has been suggested by Lahey[10] that some of the hair changes found in infants with kwashiorkor may be due to copper deficiency.

Myelin formation has been found to be abnormal in copper-deficient guinea pigs[24] and lambs.[96] It has been suggested that the involvement of copper in the synthesis of phosphatidic acids may be a partial explanation for these findings.[26]

Bone formation is also abnormal in copper-deficient animals. Changes are most striking in swine and in puppies, who show bowing, thin

cortices, deficient trabeculae, pathologic fractures, and wide epiphyses. It appears that copper may be necessary for the function of osteoblasts. Radiologic changes similar to those in puppies and swine were seen in the human infants of Cordano.[13]

Abnormalities in formation of elastin may lead to aortic rupture in fowl.[90] This effect is apparently due to the role of copper in the function of amine oxidase. In the absence of copper and pyridoxine, amine oxidase activity is decreased. As a result, lysine residues of elastin are not transformed into isodesmosine and desmosine, both of which form the elastin cross-linkages.[32]

Copper Toxicity

Copper toxicity is relatively rare in man. In animals, the chronic ingestion of excessive copper may result in hemolytic jaundice, hepatic necrosis, and death. Tolerance of rats for copper has been shown to be up to 500 parts per million (ppm), a level 100 times normal. At such an intake level, the copper content of the liver increased fourteen-fold without apparent injury.[96]

ZINC

Vallee[97] and Sullivan[91] have drawn attention to abnormalities in zinc metabolism associated with cirrhosis of the liver, while Prasad and coworkers[67, 75] and Ronaghy et al.[70] documented the effects of zinc deficiency on the growth and development of adolescent boys in Egypt (Fig. 2) and Iran. The zinc-responsive syndrome consists of dwarfism and sexual infantilism. Studies in the United States on adolescent patients with gastrointestinal malabsorption have shown their growth failure and hypogonadism also to be zinc-responsive.[8, 74]

Reports by Pories[61] and Husain[39] indicate that zinc is probably essential for wound healing in man. Studies in the zinc-deficient rat[74] support this hypothesis. A diversity of observations on zinc-deficient experimental animals suggests other clinical situations in which zinc nutriture may be important, especially maternal nutriture in relation to fetal development[37] and well being of the nursing offspring.[43]

The Function of Zinc in Higher Animals

Zinc is an essential nutrient for all species. Its two major biological functions relate to its high binding affinity for reactive sites on protein molecules. The role of zinc as a component of certain metalloenzymes is perhaps the most completely studied aspect of its biological function.[57] Zinc metalloenzymes contrast with zinc metalloproteins in that the element is firmly bound to metalloenzymes, is retained during purification, and exists in fixed stoichiometric amounts; the activity of the metalloenzyme is specifically dependent upon zinc, and removal of the metal results in loss in enzymatic activity. Examples of zinc metalloenzymes include carbonic anhydrase of human erythrocyte, carboxypeptidase A and B of bovine pancreas, alcohol dehydrogenase (horse liver), and

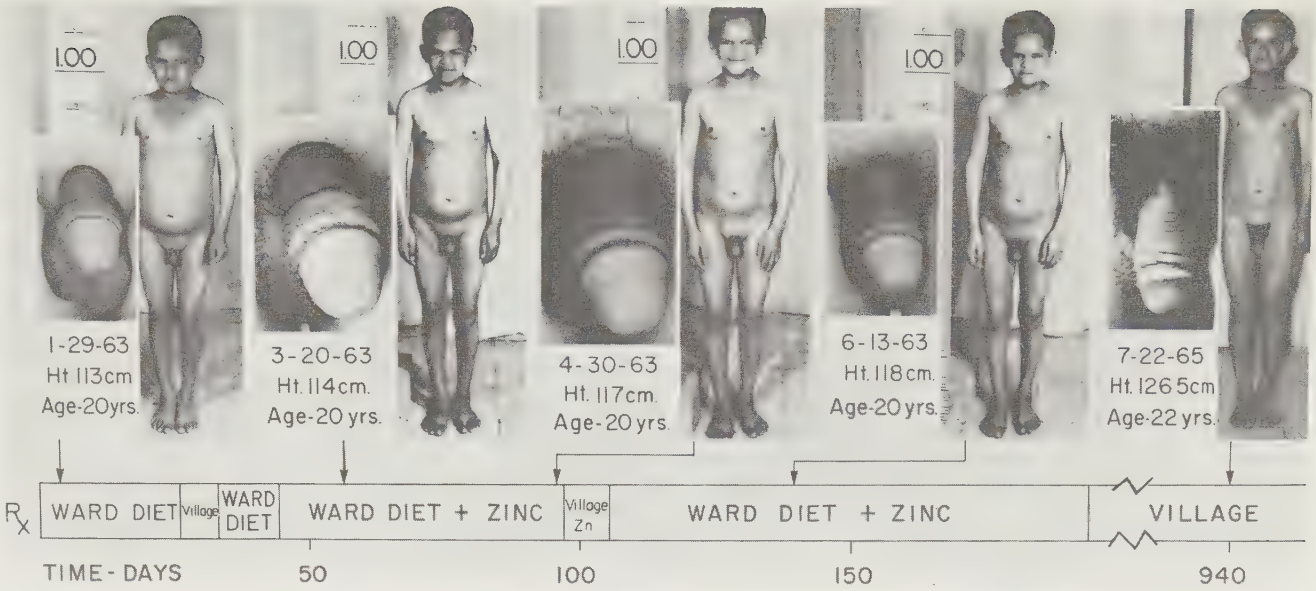

Figure 2. A 20 year old Egyptian boy with zinc-responsive hypogonadism and growth failure. When first seen on January 23, 1963, he had a bone age of 11 years. Following administration of 90 mg. of oral zinc sulfate daily for 5 months during hospitalization, he grew 5 cm. and experienced striking development of his genitalia.[75]

alkaline phosphatase (E. coli). A metalloprotein which binds zinc but whose biological function is as yet undefined is metallothionein.

A less well studied function of zinc concerns the synthesis of protein[35] and nucleic acids.[76, 92] It has been suggested that this function is mediated by its influence on ribonucleic acid molecules.[79] Zinc has been shown in vitro to restore toward normal the tertiary structure of isolated E. coli ribosomes after denaturation by treatment with EDTA.[93] It seems likely that zinc is also necessary for the conformation of mammalian ribosomes. This would at least partly explain its role in protein synthesis.

Nutritional Physiology

The North American mixed diet contains roughly 10 to 15 mg. of zinc daily, some 5 to 7 mg. of which may be retained and the remainder excreted. Availability of dietary zinc appears to be influenced by substances in the diet such as phytic acid[55] and other chelating agents (especially certain clays). Studies in rats suggest that zinc is actively accumulated by the intestinal mucosa and is slowly released into the interstitial fluid.[58] Absorption appears to be more efficient in the more distal portion of the small bowel. It has been estimated that roughly 0.25 mg. of zinc must be retained daily to accumulate the total body content of zinc of 1.9 gm. by age 20.[22] The amount required for growth of infants and children probably approximates this range.

Practically all of the plasma zinc is bound to protein (98 per cent). Although there does not appear to be a specific transport protein for zinc, it has been shown that the cation is more firmly bound to the α-1-globulin fraction than to other globulin fractions or to albumin.[65]

Tissue concentrations range from 10 to as high as 100 μg. per gm. of fresh tissue in the major soft tissues. Bone contains 80 to 150 μg. per gm., while the concentration in choroid is several times that amount. Liver and kidney contain roughly 55 μg. per gm.; prostate, epididymis, and testes may contain 100 μg. per gm. Of interest is the fact that tissue concentrations are generally constant throughout life, implying a need for a regular dietary supply for growth and the other processes that are dependent upon zinc. Studies in the rat[37] suggest that, in contrast to iron, the body stores of zinc are not readily mobile, and hence there is an unusual dependence upon a regular exogenous supply of the element.

The major route of zinc excretion appears to be the pancreatic and gastrointestinal secretions. In contrast, urinary zinc concentrations in a normal man are in the range of 500 to 700 micrograms per day, and whole sweat contains approximately 100 per liter.[65]

Effects of pregnancy, lactation, and menstruation on zinc requirements are as yet undefined. Studies in which neopartum Iranian village women were compared with Iranian middle class women suggest that zinc requirements may be increased during pregnancy.[78] Colostrum contains as much as 20 mg. of zinc per liter, while milk contains 3 to 5 mg. per liter. Requirements during lactation are therefore probably increased by an undetermined amount. Menstrual losses of zinc are estimated at roughly 0.65 mg. per 100 ml. of blood. Abnormal losses of zinc occur in patients with gastrointestinal bleeding, protein-losing en-

teropathy, malabsorption syndrome with steatorrhea, renal disease with proteinurea, and cirrhosis of the liver (increased urinary loss). These abnormal losses are reflected in the plasma zinc.[28]

The role of zinc in diabetes mellitus is unclear. Clinical studies evaluating the effect of zinc supplements in patients with diabetes mellitus have not been fruitful. On the other hand, Mills et al.[52] report that rats fed a zinc-deficient diet developed an impaired tolerance glucose. Zinc deficient humans exhibit an increased sensitivity to insulin and a variety of responses to an oral glucose tolerance test.[75]

Human Zinc Deficiency

Primary or nutritional zinc deficiency in man was first suspected by Prasad et al.[66] in 1961 when they were studying a group of 18 to 20 year old dwarfed, iron-deficient patients with hypogonadism, in Shiraz, Iran. Because their patients ate clay, they suggested that the clay had chelated dietary zinc and iron and thereby caused a deficiency of both elements. They hypothesized the possibility of zinc deficiency because of the similarity of the defect in growth and development to the syndrome of zinc deficiency in swine and other animals. In 1963 Prasad et al.[67] reported studies on Egyptian village boys with hookworm (A. duodenale) and schistosomiasis (S. hematobium and S. mansoni) which supported the zinc deficiency hypothesis. Subsequent investigations demonstrated that the observed hypogonadism and growth failure were responsive to therapy with zinc[75] and this finding has recently been confirmed by Ronaghy[69] in both male and female patients.

The major clinical features of the human zinc deficiency syndrome as it occurs in the Middle East are listed in Table 1. Patients may have all or some of these features.

The zinc-deficiency syndrome has recently been described in an adolescent male with malabsorption syndrome and hypogammaglobulinemia from New York.[8] Two young men with gastrointestinal malab-

Table 1. *Major Clinical Features of Human Zinc-Deficiency Syndrome*[67, 75]

1. Growth retardation
2. Delayed bone age
3. Hypogonadism
4. Iron deficiency due to parasitic infection and/or geophagia
5. Hepatosplenomegaly
6. Impaired growth hormone response to insulin hypoglycemia[11]
7. Impaired adrenal cortical response to exogenous corticotropin and metyrapone
8. Normal thyroid function
9. Normal intravenous glucose tolerance
10. Flat or delayed rise in oral glucose tolerance test
11. Diet: high cereal, low animal protein content
12. Zinc metabolism
    a. Decreased plasma concentration
    b. Decreased urinary and sweat excretion of zinc
    c. Rapid disappearance of injected zinc from the blood
    d. Decreased exchangeable zinc
    e. Increased rate of zinc turnover
13. Response to therapeutic zinc and an adequate diet which is far out of proportion to the response to diet alone or diet plus iron

sorption, growth failure, and hypogonadism are currently receiving therapy with zinc in Nashville, Tennessee. One, a 20 year old boy with regional enteritis, is now experiencing puberty. The second, a 17 year old boy with hypogammaglobulinemia, has shown only slight evidence of improvement after 3 months of treatment.[72]

A role of zinc in infant nutrition was inferred by Berfenstam[4] in 1952, on the basis of finding 20 mg. of zinc per liter in colostrum and 3 to 5 mg. per liter in milk. Studies in fetal,[37] neonatal,[43] and weanling[45, 76] rats confirm the fact that zinc has an important role in nutrition in early life, presumably because this is a period of rapid growth. Studies on human infants with kwashiorkor have revealed extremely low serum concentrations of zinc (about 40 micrograms per 100 ml.), which were slow to return to normal (103 ± 13 micrograms per 100 ml.) following conventional dietary therapy and care.[77] It has been suggested that the growth failure so common among infants in populations in which kwashiorkor occurs may in part be due to zinc deficiency, contributing factors being a diet low in animal products and high in cereals and other vegetable foods, from which zinc is less available. This hypothesis warrants investigation in poverty groups both abroad and in the United States, because of the important role zinc appears to play in the growth process.

Plasma zinc concentrations[28] have been reported to be decreased in neoplastic disease, tuberculosis, myocardial infarction, and cirrhosis of the liver. Prostatic zinc concentration may be decreased in association with carcinoma of that organ. Whether these findings in disease are of pathologic significance is not known.

The role of zinc in human wound healing has received considerable recent attention. Patients treated with zinc following pilonidal cystectomy are reported to have improved healing.[63] Leg ulcers unresponsive to conventional modes of treatment are also reported to heal following oral administration of zinc.[39] These observations suggest that the patients studied were relatively deficient in zinc. Studies in normal laboratory animals indicate that administration of zinc to a normal animal does not cause accelerated healing, but that the zinc-deficient rat does exhibit impairment of repair of experimental wounds (Fig. 3) and burns.[71] Clearly, more critical and more extensive investigations of these effects in man are called for. At the molecular level, zinc does appear to influence the synthesis of collagen,[43] and therefore it is not unreasonable to administer zinc to patients likely to be deficient in the cation.

Of particular interest from the developmental point of view has been the demonstration of malformations in the offspring of rats fed diets extremely low in zinc.[37] At slightly higher levels of dietary zinc (0.5 ppm), a high incidence of abortion has been noted without the occurrence of malformations or gross placental abnormalities.[73] Swenerton[92] has extended these studies to an evaluation of effects on DNA synthesis in the fetus. Incorporation of thymidine into DNA is suppressed by zinc deficiency, with an impressive decreased activity in the neural crest on the twelfth day of gestation. These studies emphasize the importance of zinc in nutrition at critical periods of growth.

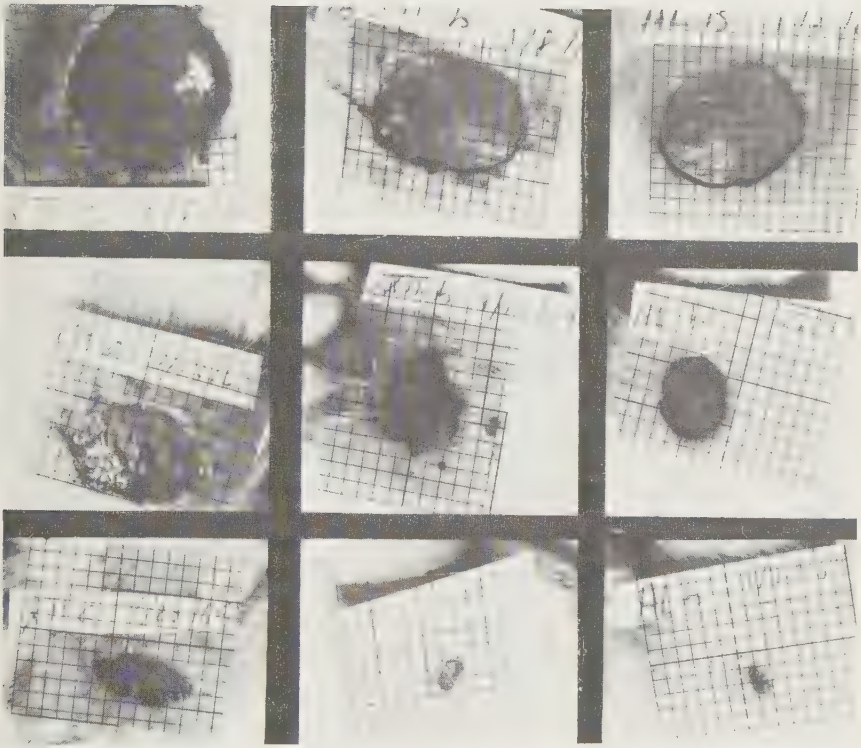

Figure 3. Effect of zinc deficiency on wound closure in the rat. The size of the ellipse of skin removed was the same in each animal. The zinc-deficient wound (XIIa) spread immediately after the skin was excised. Closure of the deficient wound was delayed compared to the pair-fed wound shown in the center panel and the ad libitum wound shown on the right.[74]

Zinc Toxicity

Zinc is a relatively nontoxic element, particularly when compared to lead, mercury, arsenic, and copper. The modes of toxic exposure are inhalation, cutaneous contact, and ingestion.[98]

Inhalation of zinc oxide fumes in high concentration, as may occasionally occur in industrial settings, produces an acute illness of relatively short duration characterized by chills, fever, leukocytosis, cough, salivation, headache, and pulmonary infiltrates. Workers may rapidly develop tolerance to the fumes and become symptom-free even while they remain at work. Intermittent exposure results in recurrence of illness.[30] Some of the colorful pseudonyms for this illness are "brass founders' ague," "galvo," "brass chills," "zinc shakes," "smelter shakes," and "metal fume fever." It has been recommended that industrial air concentrations not exceed 15 mg. per cubic meter.

Skin sensitivity to zinc oxide appears to be unusual. On the other hand, zinc chloride itself is caustic and may produce ulceration if it comes in contact with skin; this occasionally occurs when it is used as a flux in soldering.

Poisoning due to ingestion of zinc may occur when foods have been stored in galvanized containers. The threshold for taste of zinc in water is in the range of 15 ppm, while a definite metallic taste is experienced at 40 ppm. Emetic concentrations of zinc in water range from 675 to 2280 ppm. The emetic dose of zinc sulfate ($ZnSO_4 \cdot 7H_2O$) is 1 to 2 gm., equivalent to 225 to 450 mg. of zinc.

Brown et al.[6] have reported two episodes in which large numbers of people ingested food stored in galvanized tubs and punch stored in galvanized containers and became ill. Acid rinses of the food storage tubs contained more than 2500 ppm of zinc, while a 5 ounce portion of the punch contained 525 mg. of zinc, an amount within the emetic range.

The symptoms and signs of toxicity include nausea, vomiting, stomach cramps, diarrhea, and fever.

CHROMIUM

Interest in chromium exists because of its apparent effect in diabetes mellitus and other states with abnormal glucose tolerance tests. A recent review article by Mertz[50] provides an excellent discussion and bibliography of current knowledge of chromium metabolism.

Current clinical interest in chromium is based on the experimental finding that chromium-deficient rats developed diabetic type intravenous glucose tolerance tests. The rates of glucose removal is responsive to chromium supplementation. In vitro studies using epididymal fat pads from chromium-deficient rats have shown normal metabolism of glucose but decreased uptake of glucose in response to insulin. This decreased in vitro response to insulin was corrected by both in vitro and in vivo supplementation with chromium-containing compounds. In the

interactions between chromium, insulin, and the cell membrane which has been proposed, chromium is thought to form a complex between sulfhydryl groups on the cell membrane and sulfhydryl groups on the A chain of insulin.[49] On the basis of current data it is thought that chromium is a potentiator of insulin and not a hypoglycemic agent per se.

Observations on the metabolism of chromium in man suggest clinical relationships.[83] Total body content of chromium is small, less than 6 mg. Tissue levels are in the range of parts per billion. Metabolically active tissues have the highest concentrations. Geographic variations in tissue levels in man are considerable, both internationally and within the United States. The efficiency of intestinal absorption is very low, ranging from 0.5 to 3.0 per cent. In plasma, siderophilin serves as a specific transport protein for chromium. Excretion of absorbed chromium is primarily via the urine (2 to 6 micrograms per liter); a small amount is lost through the gastrointestinal tract. The dietary intake probably varies considerably, but it is estimated to be in the range of 70 micrograms per day. It is reported that in the United States there is a progressive decline in tissue concentration with age.

The production of toxic effects requires large amounts. Mertz estimates that the therapeutic:toxic ratio for intravenously injected Cr^{+3} is approximately 1:10,000.

Observations on chromium-deficient animals and data from human studies indicating low efficiency of absorption, low estimated dietary intakes, and the tendency for tissue levels to decline with age, have led to studies of human states with abnormal glucose tolerance tests. Glinsmann and Mertz[27] supplemented six maturity-onset diabetics with 150 to 1000 micrograms per day of oral chromium for 15 to 120 days and found an improved glucose tolerance in three. Short term supplementation (1 to 7 days) in another group showed no effect. Levine, Streeton, and Doisy[44] studied ten otherwise healthy elderly subjects (over 74 years of age) who showed an abnormal oral glucose tolerance test, supplementing them daily for 4 months with 150 micrograms of chromium orally. Results of glucose tolerance tests were improved in four of the ten subjects, while the other six and a control group of normal young adults showed no change.

There are two reports of studies of the effect of chromium supplementation on abnormal (diabetic type) glucose tolerance in children with kwashiorkor. Hopkins, Ransome-Kuti, and Majaj[34] reported 12 infants, six from Jordan and six from Nigeria, who responded to a single oral dose of 250 micrograms of chromium within 18 hours, with significantly improved glucose removal rates (Fig. 4). Carter et al.[9] studied 34 children with kwashiorkor and abnormal glucose tolerance tests in Cairo. No effect could be attributed to the supplement given, and all glucose tolerance curves returned to normal following 1 to 2 weeks of a high protein, high caloric diet. Carter et al. documented that the children had been exposed to chromium in many ways. It appears, therefore, that chromium deficiency may not have been an etiological factor in the abnormal glucose tolerance test in this locale. Hence, the report of Carter et al. does not controvert that of Hopkins et al.

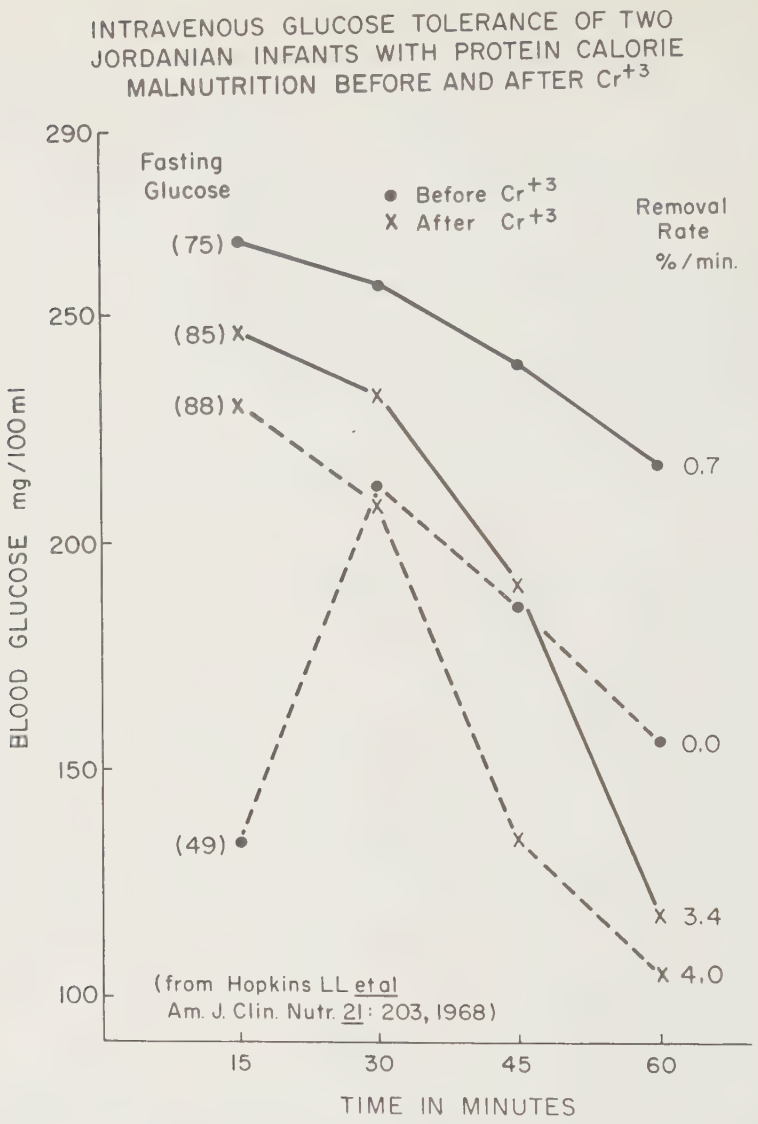

Figure 4. The response of two infants with kwashiorkor and glucose intolerance to chromium administration. The rate of glucose removal was accelerated from the peripheral blood of both infants following treatment.[34]

Current knowledge of the biological effects of chromium suggest that this trace metal may prove to be of therapeutic value in a presently unknown percentage of patients with maturity-onset diabetes, abnormal glucose tolerance tests of old age, and the abnormal glucose tolerance tests of kwashiorkor. Since chromium is only one of the many substances involved in the complex system of carbohydrate metabolism in man, it is reasonable to expect that chromium deficiency is active in only

a finite number of disturbances of this system. Thus the varied responses to chromium seen in the preliminary clinical trials are not surprising. Adequate methods of identifying those patients who may benefit from chromium supplementation and determining the most effective form of supplementation, and better understanding of the biochemical role of chromium remain to be developed before any major medical benefit can be derived from use of this trace element.

SELENIUM

Recognition of the importance of selenium in nutrition has steadily increased since 1957, when it was discovered to protect against dietary liver necrosis in rats.[88] Subsequent work has implicated selenium deficiency in many naturally occurring and experimental diseases of animals.[48, 56] Until recently, little attention had been given to selenium in human nutrition.

Dietary selenium intake is related to two factors: (1) most selenium in biological material seems to be bound to protein, and (2) certain geographical areas—including some in the United States of America—have a very low soil selenium content. Accordingly, diets low in protein and diets composed mostly of food produced in areas of low soil selenium content may be low in selenium. Little information is available concerning the selenium content of food in the United States. It seems unlikely, however, that the mixed diet is low in this element. On the other hand, it seems entirely possible that certain groups of individuals may be low in selenium. These include alcoholics who substitute alcoholic beverages for food and infants with protein-calorie malnutrition due to gastrointestinal malabsorption or primary malnutrition.

The first suggestion that selenium deficiency may occur in man appeared in 1961.[86] Significant weight gain was reported in Jamaican children with kwashiorkor who had been given selenium. A similar finding was reported from Jordan in 1967.[33] Both weight gain and a reticulocyte response were attributed to selenium administration.

Another approach to the question of selenium deficiency in man was a study of selenium blood levels in Guatemalan children hospitalized for kwashiorkor.[7] When compared to levels in a control group, whole blood and plasma selenium levels were found to be significantly lower in the malnourished children (Fig. 5). Serial measurements of blood selenium were obtained in several children who were not given selenium supplements. Even after they had recovered from kwashiorkor, their blood seleniums did not reach the normal range for months. A fairly narrow range of blood selenium levels was found in normal adults (0.22 micrograms per ml., S.D. 0.02 micrograms per ml.).

These studies suggest that human selenium deficiency may occur in protein-calorie malnutrition. It is as yet unclear what the harmful effects of deficiency are in man. It is still unknown whether morbidity in kwashiorkor is in any way related to depletion of body selenium. Further investigations of this possibility are indicated.

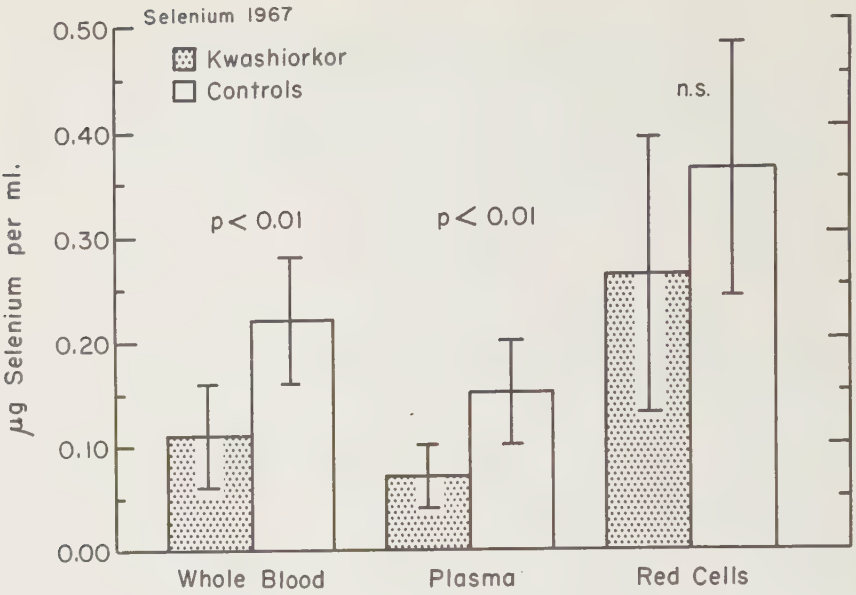

Figure 5. Children with kwashiorkor had significantly less selenium in whole blood and plasma than did controls, but not in the washed red cells. The lines enclosed by brackets represent two standard deviations.[7]

The syndrome of dietary liver necrosis in rats has been well known since the 1930's. It may be produced in weanling rats by feeding a diet deficient in both selenium and vitamin E. After about 4 weeks on the diet, the animals may die suddenly. Their livers are found to contain well-defined areas of necrosis contiguous with healthy-looking cells (Fig. 6). As little as 0.04 ppm of selenium in the diet will prevent the necrosis.

An analogous syndrome of dietary liver necrosis occurs in pigs. In its pure form, the liver is not fatty. Recently, Reid et al.[68] fed weanling pigs the necrogenic diet, with only 3 per cent protein. Both necrosis and fat accumulation occurred and the sequela was a cirrhosis which was histologically similar to that seen in man. The addition of selenium or vitamin E to the diet prevented the development of cirrhosis but had no effect on fat accumulation. These studies have prompted speculation concerning the roles of selenium and vitamin E in human cirrhosis. At present alcohol appears to be the major factor. Whether associated deficiencies of vitamin E or selenium or both contribute in some patients is unknown.

The function of selenium at the molecular level remains uncertain. There is evidence that it may act as an antioxidant, protecting membranes and sulfhydryl groups.[19, 61] If selenium does indeed function as an antioxidant, the puzzling observation that either selenium or vitamin E can prevent certain conditions in animals might be explained, since vitamin E also appears to function as an antioxidant. Selenium may also have a more specific metabolic role. This is suggested by the extremely small amounts required by experimental animals.[87]

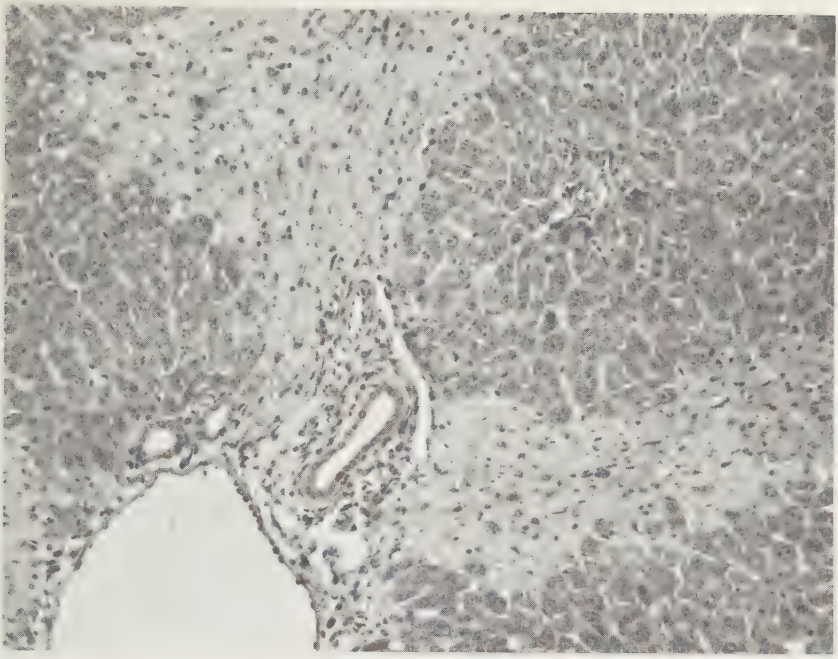

Figure 6. This photomicrograph (×80) of the liver of a weanling rat sacrificed after four weeks on a selenium-deficient and vitamin E-deficient diet demonstrates the lesion of dietary liver necrosis.

MANGANESE

The essentiality of manganese for man is inferred from animal studies.[11] An adult man contains roughly 3.5 mg. manganese per kg. body weight. Manganese with a valence of +2 activates many of the same reactions as magnesium. In vivo, however, the valence of manganese is +3, and it presumably has a different spectrum of reactions.[15]

Balance studies indicate a significant retention of ingested manganese and suggest that this is related to body size. Men[41] fed a vegetarian diet retained 37 per cent of the 7.07 mg. ingested; college women[51] retained 41 per cent of a 3.16 mg. intake; 2 year old children[99] retained 0.2 mg. per kg., or 63 per cent, of a 3.2 mg. intake. In contrast to man, birds require as much as 50 mg. of manganese per kg.

Absorption of manganese appears to be an active process, having features in common with absorption of iron. Iron-deficient rats are reported to have increased absorption of manganese.[62] Maximal absorption of Mn^{+2} occurs in the duodenum, where it is oxidized to Mn^{+3} in the mucosa. It is then bound to a specific β-1-globulin transport protein, transmanganin.

Manganese is concentrated by tissues rich in mitochondria, where it enters these organelles.[14] It appears that intracellular and extracellular manganese is maintained in dynamic equilibrium by an unknown mechanism.

The highest tissue concentrations of manganese occur in the pitui-

tary gland, the pineal gland, lactating mammary glands, liver, pancreas, gastrointestinal mucosa, kidney, and bone. Manganese in bone is found both in inorganic salts and in the cells of the organic matrix, where it appears to influence synthesis of mucopolysaccharides.[1] Manganese is also found in high concentrations in melanocytes, in which it seems to participate in the final auto-oxidation of melanin granules.[16]

Concentrations in whole blood[5] are in the range of 2.4 ± 0.8 mg. per 100 ml. (neutron activation). Roughly half of this is intracellular manganese.

Excretion of manganese is primarily via the bile, some being reabsorbed and utilized again. Urinary excretion is small, renal conservation occurring by an undefined process.

Manganese deficiency has not been recognized in man. In birds and experimental rodents, retardation of growth, structural and chemical anomalies of bone, ataxia, sterility, and anomalous fat metabolism take place. In rats, manganese is essential for successful lactation. Particularly striking in poultry are the changes in weight-bearing bones, which bow and exhibit slippage of the tendon and marked deformity of joints.[100]

Maternal manganese deficiency in rats results in abnormal development of the otic labyrinth in the young.[2] A seizure syndrome also occurs.[38] Manganese is essential for lipid metabolism; it stimulates cholesterol synthesis[17] and interacts with choline to influence the liver fat content of experimental animals. Manganese-deficient guinea pigs have been found to exhibit a decreased glucose tolerance[23] and to have decreased granulation of the beta cells of the pancreatic islets.[89]

In relation to Everson and Shrader's studies in guinea pigs, the observations of Rubenstein[71] on the hypoglycemic effects of a manganese containing decoction of green alfalfa leaves is of interest. Rubenstein studied a young Bantu who had diabetes mellitus and used this folk medication to control his blood sugar. It was found that manganese was the active principle in the alfalfa, and that oral administration of magnesium chloride caused precipitous drops in the patient's blood sugar concentrations. Studies on other diabetic patients did not produce similar effects.

An interesting relationship between manganese and a genetic disease of rats (palid strain) has been pointed out by Hurley.[36] Palid rats have an inherited defect in formation of the otic labyrinth. Hence, they lack postural orientation when blindfolded or placed in a water bath. Feeding pregnant palid rats manganese during pregnancy will prevent this inherited disease in their offspring.

Some years ago, "hydralazine disease," a syndrome resembling lupus erythematosus in dogs, was shown to be responsive to manganese administration.[12] Presumably, the hydralazine, which is a potent chelator, removed the manganese from essential metabolic sites.

Toxicity

Manganese intoxication[21] occurs in miners who inhale manganese-containing dust. The onset is insidious. Degenerative changes occur in basal ganglia, frontal lobes, and cerebellum. Patients develop ataxia, a Parkinsonian-like tremor, subjective sensory abnormalities, and psycho-

logical disorders including psychosis, weeping, and laughter. Chronic manganese intoxication in man is usually not fatal. However, relatively little improvement may occur following removal to a low manganese environment. Calcium edate therapy is said to be beneficial.

MOLYBDENUM

Molybdenum is essential for all nitrogen-fixing bacteria, including Aspergillus niger and Rhizobium sp. The requirement of higher animals for molybdenum is less easily demonstrated. The fact that an enzyme, xanthine oxidase, and certain flavoproteins contain the element implies a need.[3, 53]

Molybdenum is present in tissues in extremely low concentrations.[18] Human liver contains roughly 3.2 ppm dry weight, muscle about 0.14 ppm. Molybdenum content of tissues increases with increased dietary intake. Tissue levels of molybdenum decrease with an increased intake of inorganic sulfate, or of tungstate. Molybdenum is actively transferred across the placenta; concentrations in the fetus exceed those in the mother. Molybdenum in the blood is apparently present as molybdate and is not bound to protein.

Dietary molybdenum is readily absorbed. This is particularly true of sodium and ammonium molybdate. The primary route of excretion of molybdenum is urinary, in contrast to zinc, magnesium, and copper. Increased dietary inorganic sulfate increases the urinary molybdenum. Sulfate also tends to alleviate toxicity due to high intakes of molybdenum. In sheep it has been shown that sulfate decreases molybdenum absorption, and at the same time increases excretion. The relationships of sulfate, copper, and molybdenum in man are unknown.

A molybdenum-copper interrelationship is nutritionally important in ruminants and is economically important for man. On low molybdenum diets, copper intoxication may occur. Xanthene calculi may occur when sheep graze on low molybdenum pasture. No similar relationship is recognized in man.[96]

Molybdenum deficiency has been produced in chickens by feeding tungsten, an inhibitor of molybdenum.[31] This eventuates in decreased tissue xanthene oxidase activity, decreased excretion of uric acid with increased excretion of xanthene and hypoxanthine, growth failure, and finally death.

Molybdenum toxicity is primarily a disease of cattle. A diarrhea (teart) occurs. Other species of large animals are unaffected. Additional copper provides some protection to cattle. In addition to diarrhea, growth failure, alopecia, anemia, and bony deformities occur. In the rat, anemia, sterility, and bone deformity are prominent. As far as man is concerned, a requirement for molybdenum has not been demonstrated.

CADMIUM

Low levels of cadmium administered in long-term studies in laboratory animals[80] produce hypertension. Inasmuch as cadmium is widely

distributed in the environment (food, water and air), the question has been raised as to whether these observations may have significance for man.[81]

Rats receiving 5 ppm of cadmium in drinking water from time of weaning have exhibited chronic arterial hypertension.[80] Similarly, injection of cadmium will produce hypertension in rats.[85] Cadmium-induced hypertension in this species can be reversed by administration of zinc-sodium zinc-EDTA, as well as by other chelating agents which remove cadmium and add zinc.[84]

Prolonged feeding of cadmium to rats produces renal arteriolar and arterial lesions and glomerular changes in association with the experimental hypertension. In view of this renal effect, the variation and concentration of cadmium in human kidneys has been studied.[61] Renal tissue of the infant contains no demonstrable cadmium, but the kidney of the adult contains ten times or more per minimum measurable amount. The highest concentrations of cadmium occurred in the Japanese, and the lowest in native Africans. Among Americans, the average concentration was approximately 40 micrograms per gm. wet weight by spectrographic analysis. Schroeder[82] has reported a correlation between death from hypertensive heart disease and the degree of softness of municipal water, and between cardiovascular death rate and cadmium content of the air, and it has been reported that the cadmium content of renal tissue is higher in patients dying of hypertension than in those individuals who meet with accidental deaths.

It is evident that chronic cadmium intoxication in experimental animals leads to hypertensive disease. The evidence in man, however, remains no more than inferential.[60] Since hypertensive cardiovascular disease may result from a variety of causes, the possible relationship of environmental cadmium and cadmium which is present in renal tissue to human hypertensive disease will remain obscure until well-defined groups of patients with hypertension are studied under carefully controlled conditions, and the effect of cadmium removal by chelation therapy is ascertained.

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Metabolic Studies of Human Obesity

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Overnutrition is a major form of malnutrition in the developed countries of the world and obesity is its clearest manifestation. The risk to health associated with obesity is evidenced by actuarial statistics which indicate an increased rate of morbidity and mortality in overweight individuals. In addition to the obvious physical deformity and its resultant social and behavioral sequelae, obesity is associated with a variety of metabolic aberrations. This review will consider some of these metabolic consequences, focusing attention only upon those abnormalities of glucose, insulin, and triglyceride metabolism that are commonly associated with obesity.

Disordered Glucose Metabolism

Prominent among the metabolic aberrations associated with obesity is disordered carbohydrate metabolism. Although not an inevitable consequence of obesity, impaired glucose tolerance is often a concomitant.[23] Whether the finding of impaired glucose tolerance in these obese patients justifies the diagnosis of diabetes mellitus is not certain. The large majority of obese patients do not show clinical evidence of the generalized microangiopathy characteristic of the diabetic syndrome. Furthermore, the glucose intolerance improves and often completely disappears after weight loss.[6, 23, 24] Therefore, identification of all these individuals as diabetics may not be justified. Until a "diabetic marker" is developed which permits separation of the diabetic from the rest of the population it seems more appropriate to state that many of these obese patients just have impaired glucose tolerance.

Nevertheless, it is clear that there is some association between obesity and diabetes mellitus. The great majority of non-insulin requiring

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diabetics (those with so-called maturity onset diabetes) are overweight. Excess adipose tissue in this form of diabetes mellitus increases the severity of the glucose metabolic abnormality, and weight reduction enables easier control. Although clinically well recognized, the nature of this association between obesity and diabetes mellitus is unknown.

The observation that glucose intolerance is present in the obese state and that it is improved after loss of weight suggests that the impaired carbohydrate tolerance of obesity may be related to the presence of an increased adipose tissue mass.

Disordered Insulin Secretion and Action

Insulin resistance has long been known to be characteristic of obesity. The administration of insulin to obese individuals does not produce as a great fall in the plasma level of glucose, free fatty acid, or potassium as it does in non-obese controls.[25] The nature of this insulin resistance is unknown, although a variety of mechanisms have been postulated. Insulin antagonism, due to excessive blood levels of growth hormone or cortisol, has been proposed but not demonstrated in these obese patients in spite of extensive study.[5, 7, 8, 16, 17] At present, there is no good evidence that abnormal binding of insulin to protein can account for the insulin resistance of obesity.[7, 8] Recently it has been demonstrated that insulin is synthesized as a single molecule, proinsulin, which is later converted to insulin in the pancreas.[35] Small amounts of proinsulin are secreted into and have been demonstrated in the plasma of normal individuals.[28] However, the biological activity of proinsulin is much less than that of insulin itself.[36] These observations have led to the concept that excessive secretion into the blood of this relatively inactive form of insulin may lead to a state of relative insulin deficiency in obese individuals. However, initial studies have not demonstrated elevated levels of circulating proinsulin in obese individuals, and in this regard do not support these concepts.[38] Other studies, to be described later in this review, suggest that a defect in the ability of certain tissues to respond to normal insulin may play a role in the development of insulin resistance in obesity.[30] It is postulated that the impaired insulin sensitivity of these tissues leads to disordered glucose metabolism.

Elevated levels of plasma insulin are often, although not inevitably, found in obese individuals both in the fasted state and in response to glucose.[1, 18] The observation that hyperinsulinemia exists in the face of hyperglycemia is further evidence of the presence of insulin resistance in obesity. It should be emphasized that hyperinsulinemia may occur in obese subjects in the presence or absence of hyperglycemia, suggesting that varying degrees of insulin resistance may exist in obesity.[21]

Weight reduction in obese patients results in a fall in their plasma insulin levels, to or towards normal.[17, 30] The requirement for exogenous insulin in obese insulin-dependent diabetics also usually decreases with weight loss. These observations suggest that, like the impaired glucose intolerance already discussed, the insulin resistance of obesity may be related to the enlarged adipose tissue mass.

Abnormal Triglyceride Metabolism in Obesity

A variety of disorders of lipid metabolism have been described in obese individuals, although none have been well documented. Prominent among these are abnormalities of triglyceride metabolism. Plasma triglyceride levels have been reported to be elevated in obese subjects;[1, 6, 27, 29, 31] these studies suggest that the concentration of triglyceride in the plasma is directly related to body fatness. Although postulated, it has not yet been demonstrated that increased concentration of triglyceride in the plasma of obese individuals plays a role in their apparent predisposition to atherosclerotic heart disease. A similar but even less well documented relationship between adiposity and serum cholesterol concentration has been reported.[6] The relationship between obesity and plasma triglyceride concentration does not seem to be a simple one, for not all obese subjects have elevated levels of plasma triglyceride.[27] The level of plasma triglyceride may vary between individuals who have similar degrees of obesity. It has been suggested that factors such as age of onset of obesity and patterns of body fat distribution may account for the variability of triglyceride levels between obese individuals,[1] but it is likely that the explanation is more complex and may include the interaction of insulin, glucose, and fatty acid metabolism in the tissues and their concentration in the blood. Dietary factors may also play an important role, in particular the susceptibility of obese individuals to develop hypertriglyceridemia with high carbohydrate intake. This is suggested by the observation that patients with the syndrome of carbohydrate-induced hypertriglyceridemia (type IV, Fredrickson and Lees) are often overweight.[10] In this disorder, plasma triglyceride and pre-beta lipoproteins are elevated when dietary carbohydrate intake is high or normal. The hyperlipidemia improves or disappears after dietary carbohydrate intake is reduced. Similarly, weight loss often reduces the level of triglyceride and pre-beta lipoproteins in these patients.

Whatever the underlying mechanism, it seems evident that in many obese patients hypertriglyceridemia is related in some way to the enlarged adipose depot. The observation that weight loss and reduction in the size of the adipose depot is usually accompanied by a fall in plasma triglyceride concentration, further implicates the excessive adipose tissue mass.

THE ROLE OF ADIPOSE TISSUE IN DISORDERED GLUCOSE, INSULIN AND TRIGLYCERIDE METABOLISM, IN HUMAN OBESITY

The preceding discussion has implied that the abnormalities of glucose, insulin, and triglyceride metabolism may be related to the enlarged adipose depot. Glucose intolerance, hyperinsulinemia, and hypertriglyceridemia occur when the individual is obese and has excessive adipose tissue. With weight loss and reduction in the size of this

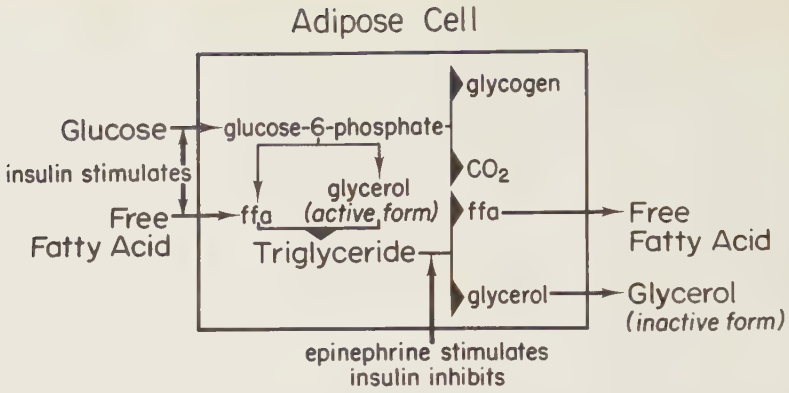

Figure 1. Schematic representation of some glucose-triglyceride metabolic interrelationships that have been studied in human adipose tissue. The effect of insulin on glucose oxidation and lipogenesis and of insulin and epinephrine on lipolysis is indicated.

tissue, these abnormalities improve or completely disappear. There is now abundant evidence indicating that adipose tissue participates actively in both carbohydrate and lipid metabolism.[11, 33] Glucose oxidation, lipogenesis, and glycogen synthesis are actively carried out in both human and experimental animal adipose tissue (Figure 1). The continuous uptake and release of free fatty acids is characteristic of adipose tissue. Hormonal influences are intimately involved in the regulation of these metabolic processes. Insulin enhances glucose uptake and its subsequent oxidation within the cell. It also influences fat deposition, stimulating both fatty acid and triglyceride synthesis from glucose (lipogenesis) and inhibiting triglyceride breakdown (lipolysis). On the other hand, the major influence of epinephrine in this regard is to stimulate lipolysis and to increase the mobilization of fat from the adipose depot. Other hormones, such as growth hormone, cortisol, and corticotropin, also influence these metabolic functions of the adipose tissue and their hormonal regulation may play a role in the development or perpetuation of the glucose and lipid metabolic abnormalities commonly seen in obesity. As a result of these observations, the morphologic and metabolic character of the adipose tissue of obese patients has been studied in an effort to determine the role of this tissue in the development of these metabolic consequences of obesity. The remainder of this paper will concern itself with a review of some of these recent studies and their possible implications.

Adipose Cell Size and Number

The adipose tissue of the normal individual gradually increases in size throughout life. This change in the size of the adipose depot is achieved by changes in the size and number of its constituent fat cells. A simple, reliable method for determining the size (lipid content per cell) and total number of adipose cells in the adipose depot has recently been developed.[12] The technique utilizes small pieces of subcutaneous adipose

tissue, obtained either by needle aspiration[13] or biopsy. Size and number of adipose cells in the tissue fragments are determined from measurement of body fat content.[22] These methods have been used to study the cellular character of the adipose depot of a large number of obese and non-obese subjects.

The adipose tissue of the normal individual grows by an increase in both the number and size of its constituent fat cells.[14] However, adipose cell number reaches its peak some time in early adult life and, thereafter, remains constant and apparently unchangeable; the subsequent growth of the adipose depot is accomplished by continued deposition of lipid in already existing fat cells (increased cell size). The age at which final adult cell number is reached and becomes fixed is not known, but the available evidence suggests that it may not be before 25 years.[9]

Obesity is characterized by the excessive growth of the adipose depot. Two types of human obesity have been described on the basis of the cellular character of the expanded adipose depot. A marked increase in the total number of adipose cells is the predominent cellular abnormality found in the expanded adipose depot of patients with one type of obesity.[14] Adipose cellular enlargement is also present but to a lesser degree. This type of obesity is usually of early onset, of severe degree, and is not easily managed by the usual dietary means. When weight loss is achieved it is accomplished by a reduction in adipose cell size but no change in cell number; the hypercellularity persists. Weight loss is almost inevitably followed by regain of adiposity, and the cycle of frustration familiar to physician and patient alike ensues. The cause of the adipose hypercellularity is unknown, although studies in experimental animals suggest that overnutrition early in life may produce similar patterns.[19] Rats overfed before weaning were fatter and larger than their underfed littermates. The excessive adiposity was found to be due primarily to an increase in the number of fat cells, and to a lesser extent to increased fat cell size. To date, this remains the only experimental model similar to this form of human obesity.[15] Adipose hypercellularity has been demonstrated early in life, in obese children,[20] but its onset has also been demonstrated to occur as late as 25 years of age.[9] A second type of human obesity has been described in which the expanded adipose depot contains enlarged but normal numbers of fat cells.[31, 34] This type of obesity is more common, is usually of milder degree, has its onset in adult life and is somewhat more readily amenable to dietary management. Weight loss is accomplished, again, by reduction in adipose cell size, without change in number. Disordered carbohydrate, insulin, and triglyceride metabolism are common to both of these forms of obesity.

The significance of adipose hypercellularity is unknown, but it may be an important etiologic factor in the development or the perpetuation of at least one type of human obesity. It is not known if and how fat cell number may influence appetite or other aspects of eating behavior. The importance of adipose cellular enlargement may lie in its influence on carbohydrate and lipid metabolism in this tissue; hence, its role in the glucose, insulin and triglyceride metabolic abnormalities seen in obesity.

Fat Cell Size and Adipose Tissue Metabolism

Since adipose cellular enlargement is common to both forms of obesity and is the only cellular characteristic altered by weight loss, adipose cell size may play a role in the development of abnormal glucose, insulin, and triglyceride metabolism shared by these obese individuals.

Several aspects of glucose metabolism in the adipose tissues isolated from obese and non-obese subjects have been examined, and these metabolic functions have been related to the size of the adipose cells in the tissue.[30, 31] Fat cell size appears to be an important factor in determining the insulin sensitivity of the tissue as measured by the degree to which insulin stimulates glucose oxidation to carbon dioxide (Figure 2). In the obese state, when adipose cells are enlarged, the adipose tissue is insulin-resistant: the ability of insulin to stimulate the rate of glucose oxidation to carbon dioxide is diminished. After weight loss and reduction of fat cell size, normal adipose tissue insulin sensitivity is restored. It has been postulated that the enlarged, insulin-resistant adipose cell may play a role in the development or perpetuation of the glucose intolerance and hyperinsulinemia commonly seen in obesity. Adipose tissue insulin resistance is present at the same time that glucose intolerance and hyperinsulinemia are demonstrable in the obese individual.[30] Reduction of fat cell size as a result of weight loss restores normal adipose tissue insulin sensitivity and, concomitantly, normal glucose tolerance and plasma insulin concentration. Insulin resistance has also been demonstrated in vivo, in the forearm tissues of individuals who have become fat and have increased their fat cell size.[16] After weight loss, normal insulin sensitivity is restored at the same time that adipose cell size is reduced. Thus, the expanded adipose tissue, through fat cell size and

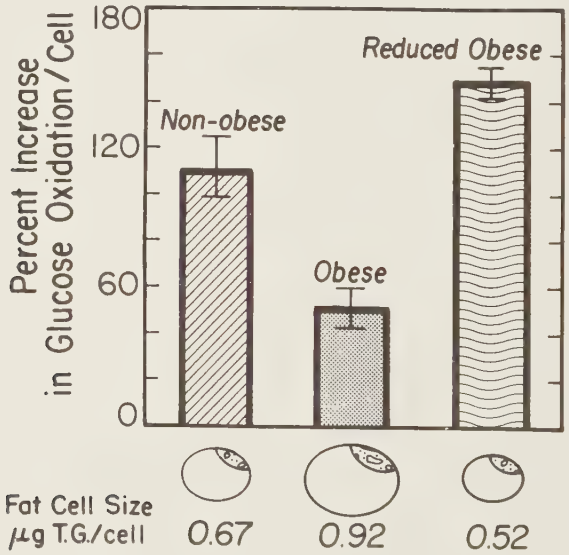

Figure 2. Insulin sensitivity of adipose tissue of non-obese and obese subjects before and after weight reduction. Insulin sensitivity is expressed as the per cent increase in the rate of glucose oxidation above the basal rate caused by insulin.

insulin resistance, may play an important role in the development of the glucose intolerance and insulin metabolic abnormalities of obesity.

Similar investigations have been made on adipose tissue triglyceride metabolism. These studies have been directed primarily toward the question of whether increased synthesis of triglyceride from glucose occurs in adipose tissue of the obese subjects, and as a result, plays a role in the development of obesity. Although some studies indicate that glucose conversion to triglyceride is increased in the enlarged fat cells of the adipose tissue of obese individuals,[31] others have been unable to demonstrate significant differences in the rates of glucose conversion to triglyceride between obese and non-obese subjects.[30] The explanation for these conflicting data is not known. It may lie, in part, in differences in dietary carbohydrate intake between the subjects studied, since it has been shown that the rate of glucose lipogenesis in adipose tissue is influenced by the carbohydrate content of the diet.[31] Whatever the explanation, it remains to be conclusively demonstrated that the rate of triglyceride synthesis from glucose is proceeding at a greater rate in the adipose tissue of obese patients when compared to that of non-obese subjects. Similarly, there is no evidence that the rate of uptake and esterification of free fatty acid in adipose tissue of obese subjects is increased.[11] Since the latter is probably the primary mechanism for triglyceride synthesis in human adipose tissue, it deserves considerable attention. To date, the effect of insulin upon glucose lipogenesis and fatty acid esterification to triglyceride in human adipose tissue has not been consistent, and therefore this important function cannot be evaluated.

A recent preliminary report has indicated that the ability of epinephrine to stimulate the breakdown of stored triglyceride (lipolysis) in the adipose tissue of obese children is impaired when compared to that of non-obese children.[20] In the face of normal or increased triglyceride synthesis, this decreased lipolysis would result in excessive accumulation of triglyceride in cells. These studies suggest one way in which abnormal adipose cell metabolism may play a role in the development and maintenance of the obese state. More definitive studies in this regard have not yet followed, but are of obvious importance to the understanding of this disorder.

The presence of enlarged insulin-resistant fat cells in the adipose tissue of obese patients may also contribute to the hypertriglyceridemia reported to occur in obesity. Studies of patients with carbohydrate induced hypertriglyceridemia (type IV, Fredrickson and Lees) indicate that the hypertriglyceridemia in this disorder may be due to stimulation of triglyceride synthesis in the liver by excessive amounts of circulating insulin.[26] It is possible, although unproven, that the presence of enlarged, insulin resistant fat cells in these obese individuals may lead to hyperinsulinemia, which in turn may act upon the liver to stimulate excessive triglyceride synthesis from glucose, and hence, hypertriglyceridemia. After weight loss and reduction of fat cell size, normal adipose tissue insulin sensitivity and plasma levels of insulin are restored, and triglyceride synthesis in the liver returns to normal.

CLINICAL LABORATORY EVALUATION OF GLUCOSE AND TRIGLYCERIDE METABOLISM IN OBESITY

Only those practical and clinical laboratory tests of glucose and triglyceride metabolism will be considered. Since measurement of plasma insulin is not readily available and is primarily a research tool, it will be excluded from this discussion.

In the absence of fasting hyperglycemia and glycosuria, the oral glucose tolerance test appears to be the most physiologic and practical current means of evaluating glucose metabolism. It should be noted, however, that the ability of the obese individual to handle an oral glucose load may vary with the load administered.[32] A dose of glucose based on ideal body weight may yield normal glucose tolerance in an obese subject, whereas administration of a glucose load based on the total body weight of that individual will almost certainly demonstrate decreased tolerance. The usual technique for performing the oral glucose tolerance test ignores this factor of adipose depot size. Thus, it is obvious that the oral glucose tolerance test as currently used is limited in its ability to define the glucose metabolism of the obese individual, let alone to establish the diagnosis of diabetes mellitus. The Committee on Statistics of the American Diabetes Association has recently recommended a set of conditions for conduction of the oral glucose tolerance test which takes into account body weight and adiposity.[2] This approach may permit standardization of this procedure and provide a basis for developing criteria upon which the glucose tolerance of an obese patient can be interpreted.

The presence of disordered lipid metabolism in obesity may be obvious on the basis of clinical manifestations such as cutaneous lipid deposits or lactescence of the serum. However, in most cases these clues will not be present and evaluation of lipid metabolism will depend upon certain laboratory tests. Determination of the fasting concentration of triglyceride and cholesterol together with the lipoprotein pattern in the plasma of obese patients will provide valuable information concerning the state of lipid metabolism. These simple and available clinical tests will uncover the existence of hyperlipidemia and help clarify its nature. If hyperlipidemia is present, the information obtained from these tests will help the physician plan the specific dietary pattern to be combined with caloric restriction in the management of the patient. For example, hypertriglyceridemia and hyperprebetalipoproteinemia suggest that low carbohydrate rather than low fat intake would be beneficial in reducing the hyperlipidemia.[10]

THERAPEUTIC IMPLICATIONS OF THESE STUDIES

Although difficult to translate into therapeutic principles, these studies may help us understand the nature of human obesity and to approach its management on a somewhat more rational, if not always successful, basis.

The observation that adipose hypercellularity is the predominent morphologic abnormality of the adipose tissue of patients with severe, lifelong obesity, may help explain some of our frustration in treating such patients. This hypercellularity apparently cannot be reversed after a certain time in life. The inadequacy of current dietary approaches to the problem of obesity may be due to their inability to effect any change in adipose tissue cellularity in adult life. Thus, the treatment of this disorder may lie in its prevention early in life through the control of factors which influence adipose cell division. Undoubtedly, one such factor is genetic. The observation that early nutritional experiences can permanently modify adipose cell number and can determine the adult character of the adipose depot suggests a more practical approach to the problem: control of feeding early in life. In this country overnutrition of the newborn and infant is the rule rather than the exception. In view of the above observations it seems germane to reconsider the concept that a "healthy baby is a big baby."

Obesity has always been considered to be a simple problem with a simple cure; overeating is the problem and dietary restriction the cure. The studies considered here indicate that obesity is instead a most complex disorder. Nevertheless, weight loss and reduction of adipose tissue in the adult individual depends upon caloric restriction and induction of negative energy balance. The importance of weight loss and reduction in the size of the adipose tissue may be more apparent in view of the study outlined. Reduction in adipose cell size and restoration of normal adipose tissue insulin sensitivity and lipid metabolism may decrease the risk of developing the abnormalities of glucose, insulin, and lipid metabolism commonly seen in obese individuals.

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The Metabolic Production and Disposal of Acid and Alkali

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Quantitative comparison of the intake of various dietary constituents with the simultaneously measured rates of excretion of the same constituents—the balance technique—has been a major investigative tool in nutrition and metabolism. This method has been extremely useful in evaluating the dietary need for and physiological control of nitrogen, sodium, potassium, calcium, and other elements in health, during growth, and in various diseases. In contrast to this long acceptance and utilization of the balance method for the study of nitrogen and mineral metabolism, the technique has been only relatively recently applied to estimate the net balance of hydrogen ions. It will be the purpose of this review to characterize the processes involved in endogenous acid production and in net renal acid excretion, and to indicate the usual dietary sources of acid and base. In addition, using the concept of hydrogen ion balance, the pathogenesis and treatment of increased input of acid or loss of base (metabolic acidosis) or increased input of base or loss of acid (metabolic alkalosis) will be discussed.

Body composition in healthy adults is essentially constant from day to day. The body stores and concentrations in body fluids of nitrogen (urea), sodium, potassium, calcium, and other electrolytes are stable. Daily intake of calories, nitrogen, and minerals is equaled by their expenditure or excretion. Similarly, the acidity and the buffering capacity of body fluids in health are stable from day to day, so that the daily production and excretion of hydrogen ions must also be equal. The nature of the buffers and the actual hydrogen ion activity or pH varies between extracellular fluid and intracellular fluid and, presumably, even in different parts of cells. Thus the body is a multi-compartmented system of fluid phases, each having differing hydrogen ion activity and each

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containing different buffers. However, only the acid-base status of the extracellular fluid is readily accessible to clinical measurement. Since the buffers of extracellular fluid are in rapid equilibrium with an approximately equal quantity of buffer within cells,[11] we can view the body operationally as being composed of a single phase, having a volume of about half the body weight (i.e., equivalent to total body water) and containing only one buffer system, the carbonic acid-bicarbonate system, by which the acid-base status of the body is generally evaluated. The ratio of carbonic acid (H_2CO_3) proportional to the partial pressure of carbon dioxide, P_ACO_2) to bicarbonate (HCO_3^-) concentration in the extracellular fluid (serum or plasma) defines the hydrogen ion activity or pH. This relation is defined in physicochemical terms by the Henderson equation, which is derived from the mass law equation for the dissociation of carbonic acid:

$$[H^+] \text{ nano Eq./L.} = K \frac{\alpha P_ACO_2 \text{ mm. Hg}}{[HCO_3^-] \text{ mEq./L.}}$$

where the dissociation constant, K = 794, and α, a combined solubility and activity constant = 0.0301 for serum at 37° C. In logarithmic form, the same relationship is given by the familiar Henderson-Hasselbalch equation:

$$pH = pK_1 + \log \frac{[HCO_3^-] \text{ mEq./L.}}{\alpha P_ACO_2 \text{ mm. Hg}}$$

where $pK_1 = 6.1$.

In health the rate of production of the volatile acid, carbon dioxide, from neutral foods such as carbohydrate, fat, and protein is equaled by the simultaneous rate of pulmonary carbon dioxide excretion, so that the arterial carbon dioxide tension (P_ACO_2), the respiratory component of the acid-base equilibrium, is held nearly constant at about 40 mm. Hg. Clearly, variations in the gradient for pulmonary carbon dioxide excretion will alter P_ACO_2, but we will not discuss in this review primary respiratory acid-base disorders.[1, 19]

Similarly, there is production each day of so-called nonvolatile or fixed acids such as sulfuric acid (H_2SO_4). As soon as such a strong acid is produced in cells by the metabolism either of ingested food or of tissue constituents, the hydrogen ions released by the dissociation of the acid react with body buffers (exemplified by bicarbonate ion) to form carbonic acid, which is transported to the lungs and excreted as carbon dioxide. The regeneration of the bicarbonate ion consumed in this buffering reaction is accomplished by the renal excretion of hydrogen ions as urinary ammonium and titratable acid, and the simultaneous excretion of the sulfate anion. For each hydrogen ion secreted into the urine by renal tubular cells, a bicarbonate ion is regenerated and returned to renal venous blood, thus restoring the bicarbonate ion consumed as the fixed acid was produced and buffered. The rate of net renal acid excretion is measured by the sum of urinary titratable acid (T.A.) plus ammonium (NH_4^+) minus any filtered bicarbonate that escapes reabsorption by tubular cells. In health the rate of production of fixed

or nonvolatile acids is quantitatively equaled by the rate of urinary net acid excretion, and the serum bicarbonate concentration, the metabolic component of the acid-base equilibrium, is maintained at normal levels of about 24 to 26 mEq. per liter. In addition, the acutely available buffer stores that defend against acid addition to the body are held steady at about 24 to 26 mEq. per liter of body water, or roughly 12 mEq. per kilogram of body weight.

The Balance of Fixed Acid Production and Renal Net Acid Excretion in Health

A series of metabolic balance studies have been carried out in normal adults eating either chemically defined diets[15] or typical North American diets.[10] Observations were made during periods when serum bicarbonate concentration and blood pH were normal and steady; the rates of renal net acid excretion were also steady, so that the daily rates of fixed acid production must have been constant as well as equal to the rate of renal acid excretion. These observations made it possible to identify the sources of fixed acid production and to quantitate their rates. The sources of fixed acid production are summarized in Table 1. These reactions identify hydrogen ions or bicarbonate ions added to or lost from the body. For descriptive purposes the reactions can be divided into three categories: (1) endogenous acid arising from neutral dietary precursors or from tissues, identified by the composition of the urine; (2) dietary content of preformed or potential acid or alkali, identified by the composition of the diet; and (3) fecal losses of potential alkali, identified by the composition of the stool.

1. Cellular Metabolism of Neutral Dietary and Tissue Constituents. The urine contains a mixture of organic acid anions. These anions arise during the metabolic production of strong acid in the body and thus serve to identify hydrogen ions added to body fluids. Not all of these anions have been individually characterized and quantitated, but in health they include normal intermediates of carbohydrate and fat metabolism such as lactate, citrate, acetoacetate, etc., that have escaped complete combustion to carbon dioxide and water, as well as normal end-products of metabolism that are generated as strong acids such as uric acid. Altogether, about 0.5 mEq. of organic acid anions are excreted each day in the urine per kilogram of body weight, or, in other terms, about 35 mEq. in an average 70 kg. adult.

In addition the urine contains inorganic sulfate that identifies the net generation of sulfuric acid during the oxidation of neutral sulfur contained in the amino acids methionine and cysteine. The excretion of inorganic sulfate thus also identifies hydrogen ions added to body fluids as strong fixed acid is buffered. Average diets result in the urinary excretion of approximately 0.5 mEq. of inorganic sulfate per kilogram body weight per day. In sum, the urinary excretion of organic acid anions together with the excretion of inorganic sulfate identify the addition to body fluids of about 1 mEq. of hydrogen ion per kilogram of body weight per day.

Table 1. *The Sources of Acid and Alkali Production and the Methods of Their Identification*

SOURCES	ADDED H^+ OR HCO_3 AND MECHANISM	METHOD OF IDENTIFYING AND QUANTITATING CONTRIBUTION
1. Cellular metabolism of neutral dietary and tissue constituents		
Carbohydrates	$\text{Glucose} \xrightarrow{O_2} 2\ \text{lactate}^- + 2\ H^+$	Measurement of urinary organic acid anions
Fats	$\text{Triglycerides} \xrightarrow{O_2} \text{acetoacetate} + H^+$	
Nucleoproteins	$\text{Nucleic acids} \xrightarrow{O_2} \text{urate} + H^+$	
Sulfur-containing amino acids	$\text{Methionine} \xrightarrow{O_2} \text{urea} + CO_2 + H_2O + SO_4^= + 2\ H^+$	Measurement of urinary inorganic sulfate
2. Dietary intake of preformed or potential acid or alkali		
Phosphoproteins	$\text{Phosphoserine} \xrightarrow[\text{at pH } 7.4]{H_2O} ROH + \frac{0.8\ HPO_4^-}{0.2\ H_2PO_4} + 1.8\ H^+$	Net quantity identified by the difference between the sum of $(Na^+ + K^+ + Ca^{++} + Mg^{++})$ minus the sum of $(Cl^- + 1.8\ P)$ in the diet (= dietary cations − anions)
Phospholipids	$\text{Lecithin} \xrightarrow[\text{at pH } 7.4]{H_2O} ROH + \frac{0.8\ HPO_4^-}{0.2\ H_2PO_4^-} + 1.8\ H^+$	
Metabolizable cations (NH_4Cl, arginine·HCl, etc)	$R\text{-}NH_2^+\ Cl^- \xrightarrow{O_2} \text{urea} + CO_2 + Cl^- + H^+$	
Metabolizable anions (K^+ citrate, Na^+ lactate, etc)	$R\text{-}COO\ K^+ \xrightarrow{O_2} \text{urea} + CO_2 + K^+ + HCO_3^-$	
3. Fecal loss of actual or potential alkali	Fecal loss of $K^+\ HCO_3^-$ or of K^+ acetate$^-$, proprionate$^-$, butyrate$^-$, etc	Net quantity identified by the difference between the sum of $(Na^+ + K^+ + Ca^{++} + Mg^{++})$ minus the sum of $(Cl^- + 1.8\ P)$ in the feces (= fecal cations − anions)

2. Dietary Intake of Preformed or Potential Acid or Alkali. Fruit, vegetables, milk, and coffee contain inorganic cations in excess of inorganic anions. This excess of cations identifies the presence in these foods of organic anions such as citrate, lactate, etc. that are metabolized to bicarbonate and thus represent the intake of potential alkali. Meat, because of its content of phosphoproteins, and eggs, because of the phospholipids of the yolk, contain inorganic anions in excess of inorganic cations. This excess of anions identifies the presence in these foods of organic cations such as ammonium that are metabolized to urea and hydrogen ions and thus indicate that intake of potential acid. When all the foods contained in an average North American diet are analyzed in these terms, the diet is found to contain a net excess of inorganic cations.[10] The quantity of potential alkali thus ingested in a general diet approximates 1 mEq. per kilogram body weight per day, or about 70 mEq. in an adult of average weight. Clearly, however, the quantity of potential acid or alkali ingested in the diet will depend on the types and quantities of different foods eaten, and these, in turn, will be determined by individual dietary habits. Only a crude estimate of the range of potential acid or alkali in the diet can be given. In diets containing a large proportion of meat and eggs, as much as 50 mEq. of potential hydrogen ion might be ingested, whereas diets consisting primarily of fruits and vegetables might provide as much as 200 mEq. of potential bicarbonate.

3. Fecal Loss of Actual or Potential Alkali. The feces contain inorganic cations in excess of inorganic anions. The stool water has been shown to contain about 40 mEq. per liter of bicarbonate and an average of about 180 mEq. per liter of organic anion, principally acetate, as well as other short chain fatty acid anions.[21] These organic anions also may be viewed as representing the net fecal loss of potential bicarbonate. In adults eating typical diets, about 100 to 150 gm. of feces containing about 35 mEq. of organic anion including bicarbonate are excreted each day. In health the quantity of organic anion appears to vary in rough proportion to the organic anion content of the diet, but the feces still contain an excess of organic anion, indicating alkali loss even in subjects eating diets that contain an excess of organic cation that indicates acid ingestion.[9]

The Acid Balance

The reactions just described thus allow identification and quantitation of the overall dietary and metabolic reactions contributing hydrogen ions or base (bicarbonate) to the body each day. In health, when the state of titration of body buffers is normal and stable as shown by normal serum bicarbonate and blood pH levels, the rate of fixed acid production is equalled by the rate of renal net acid excretion:[10]

Net fixed acid production = Renal net acid excretion

[Urinary organic anions + inorganic sulfate] − [(Dietary inorganic cations-inorganic anions) − (Stool inorganic cations-inorganic anions)] = Urinary titratable acid + ammonium − bicarbonate.

Using these concepts, the processes involved in the pathogenesis of metabolic acidosis or alkalosis may then be viewed as resulting from

alterations in the rate of acid production relative to the rate of renal net acid excretion or the converse.

METABOLIC ACIDOSIS

Metabolic acidosis is characterized by reduction in blood pH or elevated hydrogen ion activity, decreased serum bicarbonate concentration, and a compensatory physiological decrease in $P_{A}CO_2$. The processes resulting in the development of metabolic acidosis are outlined in Table 2. The four major mechanisms include: (1) increased ingestion of acid or potential acid as in ammonium chloride poisoning, (2) increased cellular fixed acid production as in diabetic ketoacidosis, etc., (3) increased losses of base from body fluids exemplified by diarrheal losses of bicarbonate and organic anions, and (4) reduced renal net acid excretion. More than one such process may often operate simultaneously. For example, diarrheal losses of base are accompanied by concomitant losses of water, sodium, and chloride that may lead to significant extracellular volume depletion and functional renal failure (prerenal azotemia), or a patient with chronic renal failure may develop a complicating gastroenteritis with diarrhea.

The severity of metabolic acidosis, as assessed by the degree of reduction in serum bicarbonate concentration, depends on the rate of development of the acidosis-producing process, as well as on the ultimate magnitude of the acid load relative to the capacity of the kidneys to excrete acid. Some perspective is provided by a consideration of both clinical and experimental studies of acidosis. As previously described, diets do not contain large quantities of preformed or potential acid. However, fixed acid production has been experimentally increased by oral feeding of potential acid to normal subjects. When acid production is increased by 2 to 3 mEq. per kilogram body weight per day as a result of the continuous oral administration of methionine[8] or ammonium chloride,[7] serum bicarbonate concentration falls progressively during

Table 2. *Mechanisms in the Development of Metabolic Acidosis*

I.	Increased *net* fixed acid production
	A. Increased endogenous acid production
	NH_4Cl poisoning (or ingestion of HCl, arginine monohydrochloride)
	Diabetic ketoacidosis
	Lactic acidosis
	Ketoacidosis of starvation
	Ethylene glycol poisoning
	Paraldehyde poisoning
	B. Alkali loss
	Diarrhea
	Ureteroenterostomy
II.	Decreased renal *net* acid excretion
	Chronic renal failure
	Renal tubular acidosis
	Acetazolamide therapy

the first 3 or 4 days of acid loading as renal net acid excretion rises. Subsequently, serum bicarbonate concentration is observed to stabilize at levels 4 to 6 mEq. per liter below normal (i.e., 18 to 20 mEq. per liter) despite maximum increments in the rate of renal net acid excretion. Thus it appears that serum bicarbonate concentrations decline about 2 mEq. per liter for every 1 mEq. per kilogram body weight per day increment in acid production. There are recent animal studies that suggest that the nature of the administered acid also affects the severity of the ensuing acidosis, a given dose of hydrochloric acid causing a greater reduction in serum bicarbonate than equivalent doses of sulfuric acid.[6] However, this effect has not yet been documented in man. In the mild ketoacidosis of starvation, serum bicarbonate levels are also generally observed to be reduced by 2 to 4 mEq. per liter, reflecting an increase in acid production of 1 to 2 mEq. per kg. per day.

In contrast to these relatively moderate increments in rates of acid production, generation of acetoacetic and hydroxybutyric acids in uncontrolled diabetes mellitus or the production of lactic acid in shock may reach rates of approximately 10 mEq. per kg. per day or more within a few hours. Similar rapid rates of endogenous acid production are seen in ethylene glycol poisoning, due in part to oxalic and glycolic acid accumulation,[3] and in paraldehyde poisoning in which the nature of the acid has not yet been determined.[5] A rare example of such a large increase in acid production as the result of potential acid ingestion is that of a woman who is estimated to have ingested more than 10 mEq. per kg. of ammonium chloride and was observed to have a serum bicarbonate of 2.0 mEq. per liter and blood pH of 6.78.[16]

Reductions in the rate of renal net acid excretion generally result in less severe degrees of metabolic acidosis. In patients with uncomplicated and untreated oliguric acute renal failure, in whom renal acid excretion is virtually nil, serum bicarbonate concentration is usually observed to fall by 1 to 2 mEq. per liter per day. This decline reflects the ongoing addition of fixed acid to body fluids at a rate of 0.5 to 1.0 mEq. per kilogram body weight per day as organic acids and inorganic sulfate are formed by tissue catabolism. In such circumstances the development of and the severity of the acidosis may, of course, be accelerated by associated increases in the rate of tissue breakdown as a consequence of crushing injuries or infections and fever. In patients with chronic renal failure, metabolic acidosis results primarily from impaired renal ammonium excretion, although occasionally a reduced threshold for renal tubular bicarbonate reabsorption with urinary bicarbonate wasting may also play a role.[17] Acid production is not increased.[4] Generally, such patients appear to develop only moderate degrees of acidosis with blood bicarbonate levels in the 15 to 20 mEq. per liter range. This stabilization of blood bicarbonate concentration at tolerable levels appears to be the consequence of several mechanisms: (1) buffering of acid by alkali contained in the skeleton, a mechanism brought into operation by chronic acidosis;[11] (2) perhaps by the self-selection of diets containing more potential alkali (more fruit or vegetables and less meat); (3) by the small residual capacity of the kidneys to excrete acid. When patients with

renal disease exhibit more severe degrees of acidosis, another process is usually present, such as diarrhea, starvation, infection with accelerated tissue catabolism, etc., which accelerates the rate of *net* acid production.

Metabolic acidosis associated with uncomplicated diarrheal diseases is generally not severe. Serum bicarbonate concentrations on admission averaged only 18.1 mEq. per liter in the extreme example of adults with cholera who subsequently excreted, during the first day of treatment, more than 3 liters of watery stool containing 40 mEq. per liter of bicarbonate.[20]

In treating metabolic acidosis, initial attention should be directed toward reduction of accelerated rates of acid production or alkali loss, depending on the cause of the acidosis. Insulin is required to correct the biochemical defect(s) resulting in diabetic ketoacidosis, therapy of the acidosis alone being futile. Appropriate therapy of shock is necessary to restore adequate tissue perfusion and oxygenation and to eliminate lactic acid production. The acidosis should be treated with sodium bicarbonate if the cause of the acidosis cannot be attacked directly, as occurs in the temporary but ongoing fecal loss of alkali in severe diarrhea, or if impaired renal net acid excretion is a major factor in the patient's illness. In addition, acidosis should be treated specifically in any circumstance if the degree of acidosis is severe (pH < 7.15, bicarbonate < 12 mEq. per liter). Sodium bicarbonate should be infused intravenously, giving about 0.5 mEq. per kg. body weight (1.0 mEq. per liter body water) per 1 mEq. per liter reduction in serum bicarbonate. This should be infused over 4 hours to raise serum bicarbonate to the range of 10 to 12 mEq. per liter in patients whose original bicarbonate levels are less than 10 mEq. per liter and to about 16 to 18 mEq. per liter in patients with initial bicarbonate levels of 10 to 12 mEq. per liter. More rapid correction of acidosis may produce tetany. Treatment of the acidosis in patients with chronic renal disease has not been evaluated by controlled studies but maintenance of normal serum bicarbonate levels by the continuous oral administration of sodium bicarbonate has been shown to prevent the negative calcium balance that is a feature of renal failure and possibly a contributory factor in the pathogenesis of renal osteodystrophy.[11] Generally, it is the more common practice to maintain serum bicarbonate levels at about 20 mEq. per liter in these patients by the oral administration of sodium bicarbonate, taking into account associated hypertension or congestive heart failure. Full correction of the acidosis by sodium bicarbonate therapy is required in patients with primary renal tubular acidosis to prevent recurrent nephrolithiasis and bone disease.[2]

METABOLIC ALKALOSIS

When we turn to a consideration of metabolic alkalosis, which is characterized by an increased blood pH or diminished hydrogen ion activity, elevated serum [HCO_3^-] concentration, and a slight compensatory increase in P_{CO_2}, we must consider two phases of the disorder. First, we must consider the processes which produce the alkalosis, and

secondly we must consider the mechanisms responsible for the subsequent maintenance of the alkalosis. The processes involved in the production of metabolic alkalosis are usually fairly easily explained, but the reasons for the subsequent persistence of the alkalosis, i.e., the continued high serum bicarbonate concentration (or in other terms, the elevation of the renal threshold for bicarbonate) have been a matter of dispute for some time.

Some of the processes which are responsible for the development of metabolic alkalosis are listed in Table 3. In general they include excessive ingestion of alkali, hydrogen ion loss, and increased renal net acid excretion. In earlier days, when chloride was considered to be an "acid anion," the pathophysiologic explanation for the alkalosis associated with vomiting was accepted simply as being depletion of the "acid," chloride. However, in current views of acid-base physiology, it is recognized that chloride is in fact a very weak base (has little affinity to combine with hydrogen ions) and does not donate hydrogen ions to body fluids. Thus, this earlier explanation is not valid. We shall return to the specific role of chloride in the maintenance of alkalosis subsequently. Of the mechanisms listed in Table 3, it is likely that the physician is most apt to see metabolic alkalosis that either is due to loss of acid gastric juice or is a result of diuretic therapy. Excessive ingestion or administration of $NaHCO_3$ or $CaCO_3$ appears to cause systemic alkalosis only if there is some impairment of urinary bicarbonate excretion consequent to reduced renal function.[12]

The original production of the negative hydrogen ion balance in gastric alkalosis is due to the hydrogen ion lost from the gastrointestinal tract. At pH 1, approximately 100 mEq. of hydrogen ion per liter of gastric juice are secreted by the parietal cells of the stomach. This hydrogen ion is, of course, ordinarily reabsorbed further down the intestine, and thus no external loss of hydrogen ion ensues. The loss of acid gastric juice by vomiting or by nasogastric suctioning will obviously lead to diminution in hydrogen ion concentration (i.e., increased pH) and a rise in serum bicarbonate concentration in body fluids. It is worth noting that the negative potassium balance and hypokalemia associated with gastric alkalosis is not simply due to a loss of potassium in gastric secretions but is primarily a result of the loss of potassium into the urine consequent to the systemic alkalosis.

Table 3. *Mechanisms in the Development of Metabolic Alkalosis*

I. Increased *net* alkali production
A. Increased alkali intake
Milk-alkali syndrome or sodium bicarbonate ingestion (with impaired renal function)
B. Acid loss
Vomiting
Chloride-losing diarrhea of infancy (rare)
II. Increased renal *net* acid excretion
Diuretic drug therapy
Aldosteronism
Cushing's syndrome

Ordinarily, diarrhea results in metabolic acidosis owing to loss of bicarbonate and potential bicarbonate as organic anion in the stool, as described earlier. However, there have been a few reports of an unusual disorder of "congenital alkalosis with diarrhea and chloride-free urine."[13] Increased fecal losses of hydrogen ion have not been documented in these cases, but there is excessive fecal loss of chloride and it is likely that the persistence of the alkalosis in these rare individuals is the result of the depletion of chloride (vide infra). The mechanism(s) for the alkalosis of aldosteronism and Cushing's disease have not been completely elucidated. It appears that an interplay of several factors, including severe potassium depletion and hormonal excess, account for the disorder and that increased renal net acid excretion is the final common pathway. The pathophysiologic processes which result in elevated serum bicarbonate concentration during diuretic therapy are also not well established, but ultimately the alkalosis results at least in part, from increased renal net acid excretion.

Ordinarily, serum bicarbonate concentration is kept constant at 24 to 26 mEq. per liter, bicarbonate disappearing from the urine when serum bicarbonate concentration falls below this threshold level and a bicarbonate diuresis ensuing when serum bicarbonate concentration rises above it.[14] However, both in gastric alkalosis and in diuretic-induced alkalosis, serum bicarbonate concentration remains elevated without bicarbonate appearing in the urine (i.e., the urine remains acid). The roles of potassium depletion, sodium (extracellular volume) depletion, and chloride depletion in accounting for the persistently elevated renal bicarbonate threshold in metabolic alkalosis have been extensively investigated in the last several years. Although earlier studies had suggested that the maintenance of metabolic alkalosis was a consequence of potassium depletion, more recent evidence has shown that alkalosis resulting from loss of acid gastric secretions, as well as diuretic-induced alkalosis, can be fully corrected by the administration of sodium chloride alone, despite continuing hypokalemia and negative potassium balance. In addition, potassium administered with any anion except chloride (such as preparations of potassium gluconate, acetate, etc.) results neither in correction of the alkalosis nor repair of the potassium defecit.

In a series of experiments aimed at elucidating the role of anions in general, and chloride in particular, it has been concluded that, in fact, chloride depletion accounts for the persistence of metabolic alkalosis and an elevation of the renal threshold for bicarbonate.[18] Chloride depletion is felt to produce its effect by accelerating hydrogen ion and potassium secretion in the distal renal tubule accounting for persistent aciduria as well as continued potassium loss. It is clear, however, that for chloride depletion to produce this acceleration of the distal exchange mechanism, which normally reabsorbs Na^+ in exchange for H^+ and K^+, there must be a concomitant demand for sodium reabsorption, and it is likely that the persistence of the alkalosis involves an interplay of both the need for sodium conservation and the availability of chloride.

These concepts are relevant to the therapy of metabolic alkalosis. If the original process leading to the development of alkalosis is stopped

(for example, discontinuation of nasogastric suction) and the patient is then able to ingest a normal diet containing sodium chloride or is given parenteral fluids containing salt, the retention of hydrogen ions generated endogenously (vide supra) together with chloride will result in correction of the alkalosis within a few days. Similarly, discontinuation of alkali administration or diuretic therapy will also result in return to normal acid-base status by this same process, again assuming intake of a normal diet. Treatment of metabolic alkalosis with acidifying agents such as ammonium chloride or arginine monohydrochloride is rarely, if ever, needed. Patients with congestive heart failure, eating a low salt diet, may develop metabolic alkalosis while on diuretics. Additional sodium often cannot be given and the diuretics cannot be discontinued. These individuals must be given a source of chloride in order to repair the alkalosis. It should be given as potassium chloride so that associated potassium deficits can also be corrected, particularly in patients taking digitalis.

Finally, there also appears to be a small number of patients with so-called "saline-resistant metabolic alkalosis," in whom alkalosis persists despite the presence of chloride in the diet and in the urine. This situation may be observed in patients with primary aldosteronism or Cushing's syndrome as well as in a very few patients with unusually severe degrees of potassium depletion. The mechanism for the persistence of alkalosis in these patients has not been identified.[18]

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New Knowledge of Nutrition and Dental Health

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The very high frequency of dental caries and periodontal disease and the tremendous need for dental care observed in various areas of the United States during the recent National Nutrition Survey have brought to public and governmental attention the urgency for immediate national concern to improve oral health. In the final report of President Richard Nixon's White House Conference on Food, Nutrition and Health,[38] a strong plea was presented for the inclusion of the fundamentals of nutrition in the required portion of every dental curriculum, and for elective nutrition courses to be offered. In addition, the recommendation was made that federal financial support be provided to enable dental schools to establish or expand nutrition units and to offer graduate and postdoctoral training in nutrition.

GENERAL RELATIONSHIPS OF DIET AND NUTRITION TO ORAL TISSUES

It is certainly not fortuitous that the almost universal prevalance of dental caries and periodontal disease among the American people should have become so dramatically evident during this nutrition survey, and that the White House Conference should have expressed concern through their recommendations. Research of recent decades has clearly demonstrated the intimate relationships of the choices and composition of our foods to both dental caries and periodontal disease. Each of these chronic diseases has a complex etiology, with involved interrelationships among three parameters: a microbial agent or agents; the proneness of the host and the tissues to the disease processes; and the oral environment around the teeth and their supporting structures.

Nutrition is related to oral health through the many metabolic pathways responsible for the development and maintenance of the various oral structures. The proneness of the latter to disease is dependent in

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varying degrees upon these pathways; i.e., they contribute to the host factor in the epidemiological triad of agent, host, and environment. However, in addition, nutrition is related to oral health through dietary interactions at the surfaces of the erupted teeth and the gingival margins. Thus, oral problems have an additional dimension with respect to our food composition and eating patterns, beyond those of problems of nutritional origin elsewhere in the body. These facets contribute to the environment around the teeth and the supporting tissues in which microbial agents live and metabolize. Through appropriate dietary procedures these disease processes can be altered as to both initiation and rapidity of progression by increasing the resistance of the host or by reducing the disease-producing potential of the environment.

The picture is further complicated by the biological nature of the dental tissues which are destroyed by dental caries and periodontal disease. The acellular enamel and dentin of erupted teeth have no reparative ability. The periodontal tissues, the supporting structures of the teeth, have relatively limited ability to regenerate themselves when the active disease process has been arrested.

The relationship of various severe and prolonged nutritional deficiencies to the development and maintenance of the various tissues and organs of the mouth, and associated structures such as the major and minor salivary glands, closely parallels their relationship to tissues of comparable origin elsewhere in the body. Possibly, oral tissues reflect nutritional deficiencies more readily because of the greater mechanical, chemical, and thermal stresses to which they are subjected during the processes of mastication and swallowing. In addition, the mouth is the habitat of a great many types of microorganisms which are grouped in several microcosms within the mouth in accordance with their biological characteristics. The microflora is largely dependent upon food retained in the mouth for provision of the needed nutrients for growth and multiplication.

Detailed descriptions of the oral manifestations of scurvy, pellagra, ariboflavinosis, and multiple B-complex deficiencies have been presented in various nutrition textbooks.[15] The florid oral evidences of these nutritional deficiencies were prevalent in many areas of Canada and the United States during the early decades of nutritional science, but now have almost completely disappeared from the scene owing to the greater personal and governmental awareness of nutritional needs and to food fortification programs. Careful search for these signs should be included in every physical and dental examination. When such oral nutritional problems are observed, they are usually associated with parental neglect, alcoholism or mental deficiency, geographic isolation from a varied food supply, or economic and housing inadequacies of the elderly, or they are secondary to medical problems or inadequately functional natural or artificial dentures.

NUTRITION AND TOOTH DEVELOPMENT

Early in the history of nutrition as a science, deficiencies or imbalances in nutrient intake were observed to influence the integrity of

the tissues responsible for the development of the teeth of experimental animals. Vitamin A deficiency resulted in atrophy of the ameloblasts, the cells of ectodermal origin responsible for the elaboration of the enamel matrix.[27] Vitamin C deficiency caused reduction in and finally cessation of metabolic activity of the odontoblasts the cells of mesodermal origin which form the dentin.[27] No evaluation has been made of any possible influence of vitamins A and C deficiency during tooth development in proneness to dental caries. Deficiencies or imbalances of vitamin D, calcium, and phosphorus resulted in imperfect mineralization of the enamel and dentin.[27] Some investigators believed that these mineralization problems resulted in teeth with greater proneness to dental caries activity. The likelihood is small that any of these deficiencies occur sufficiently severely to cause significant problems of gross malformation or disease susceptibility in industrial nations. However, in developing countries the high frequency of linear hypoplasia of the deciduous incisors[36] and greater dental caries activity in deciduous teeth compared to permanent teeth may have a nutritional component.[26] For example, in a Nigerian village where kwashiorkor and malaria are major health problems, eruption of deciduous teeth was delayed and 21 per cent of 420 village children aged 0 to 4 years had hypoplastic enamel.[9] No enamel hypoplasia was observed in 113 control children in a similar ethnic group of higher economic and educational status. Delayed exfoliation of the deciduous teeth and retarded eruption of the permanent teeth have been reported as a result of wartime dietary restrictions in Norway and other European countries.[37]

Studies with experimental animals have shown that nutritional status during tooth development can influence the chemical composition and size of the teeth, the shape of the cusps and fissures, the time of tooth eruption and the proneness of the teeth to decay. One of the most striking demonstrations of the influence of nutrition on tooth development concerns the use of a borderline protein deficient diet throughout the reproductive cycle of rats.[29] When offspring are transferred to an adequate diet after weaning, they do not attain normal body sizes or skull dimensions, their teeth are smaller than normal and have a higher proneness to caries than is typical, and the third molars erupt significantly late and have altered cuspal patterns, in many cases involving a missing cusp.

The dietary component which has been shown to have the greatest influence upon resistance to dental caries during tooth development in man is unquestionably fluoride. The ingestion of an optimal amount of fluoride throughout the complete period of tooth development results in a reduction of about 60 per cent in the incidence of dental caries. The benefit is greatly reduced when fluoride is not made available until the teeth have erupted. The source of the fluoride does not appear to be important. Fluoridation of a public water supply at the appropriate level for the climatic characteristics of a community has proven to be highly effective with regard to dental benefits, as well as inexpensive and safe.[20] Consumption of the same amount of fluoride from a proprietary product alone[1] or with vitamins or from fluoridated salt has also been shown to be effective.[19] These procedures have now been evaluated and found to

be equally effective in many locations within the United States and Canada as well as in numerous other countries where widely different dietary practices, ethnic, cultural, geographic, and climatic variables prevailed. At the end of 1969 in the United States, 2653 water supplies were providing controlled fluoridation to 80 million people.[10]

When fluoride is provided in optimal amounts in some items of the diet during tooth development, fluoride concentration in the enamel and dentin increases beyond the levels observed in low fluoride areas.[5] Fluoride becomes an integral component of the hydroxyapatite crystal lattice of which the mineral component of all skeletal tissue is composed. Observations in bone indicate that the size and degree of perfection of these crystals increase with increased amounts of fluoride.[39] These changes in the composition and nature of the crystals are considered to result in decreased acid solubility and thereby increased resistance to dental caries. The distribution of fluoride in tooth substance is especially interesting, with the concentrations in dentin being 2 to 3 times those of enamel, but a more interesting fact concerns the distribution of fluoride within the enamel.[15] When a tooth erupts into the oral cavity the very outermost layer of enamel has a very high fluoride concentration compared to the deeper levels of enamel; the difference often is in the neighborhood of eight times or more. The external surface of the enamel continues to absorb fluoride from the oral fluids for several years after eruption when a plateau is reached; however, little or no increase in fluoride concentration is observable in the deeper levels of enamel. Since carious lesions originate on the outer surface of the enamel at the interface with the oral environment, the high surface concentration of fluoride is thought to be of great importance with respect to resistance to dental caries.

The topical application of fluoride solution or gels containing fluorides to the surfaces of the teeth in the dental office results in increased fluoride in the surface enamel and reductions in dental caries.[21, 33] The level of benefit has been less than with fluoridation of public water supplies, and the procedure is costly because of the amount of professional time involved and the necessity for periodic applications. The use of fluoride-containing dentifrices has also been shown to reduce dental caries, although less effectively than topical fluoride application, even when its use is carefully supervised to insure sufficiently frequent and intimate application. While both topical fluoride and fluoridated dentifrice are clearly worthwhile where water fluoridation is not available, or even as supplemental procedures to water fluoridation, the levels of their effectiveness are so far below that of water fluoridation that they are clearly inadequate alternatives.

Other trace elements with caries-inhibiting properties have been sought but as yet without success. Among these molybdenum and vanadium have attracted the most interest. From epidemiological correlations, selenium has been suggested as a possible element which might cause increased dental caries experience in human populations.

In rodents, the feeding of diets with grossly altered calcium-phosphorus ratios during tooth development results in alterations in the carbonate content of the enamel and dentin.[32] This change is of interest

because increased concentrations of carbonate in synthetic hydroxyapatites increase acid solubility. In addition, an inverse relationship has been reported to exist between fluoride and carbonate concentrations in human teeth.[22]

While the safety and the dental benefits of optimal fluoride ingestion have been abundantly demonstrated on varied ecological scenes, additional facets of potential contribution to human health need to be investigated. During the Framingham heart studies, the frequency and severity of osteoporosis exceeded the levels expected.[18] The hypothesis was advanced that this problem of bone metabolism might be related to the low level of fluoride available for ingestion throughout the lifetime of the citizens in that area. The first epidemiological evaluation of this hypothesis was made in North Dakota. Adults 45 years and older in communities with low concentrations of water-borne fluoride (0.15 to 0.3 ppm) were compared with representative people in a similar group of communities where the water supplies contained larger amounts of fluoride (4.0 to 5.8 ppm). The latter communities had water-borne fluoride levels well in excess of that recommended for optimal dental benefits without mottled enamel.[3] The frequency of normal bone density in the high fluoride communities was consistently higher for each age group than in the low fluoride towns. The differences were statistically significant for women in the 55 to 64 and 65+ year age group ($p < 0.01$) and for the men in the 55 to 64 year age group ($p < 0.05$). In these age groups the frequency of decreased bone density in both high and low fluoride areas was greater for women than for men.

A higher frequency of collapsed vertebrae was observed in the women of the low fluoride communities than in those from the high fluoride communities. These differences were significant for the 55 to 64 and the 65+ age groups. A much higher prevalence of collapsed vertebrae was observed among the men than among the women in both high and low fluoride areas, but no statistically significant difference was observed between the areas. The high occurrence of collapsed vertebrae among the men was thought to be attributable to the fact that many were farmers who had been engaged in very heavy work.

Another finding concerned the higher prevalence of radiologically detectable calcification in the abdominal aorta in all age groups in the low fluoride areas than in the high fluoride areas. This trend was especially clear among the males, with statistically significant differences for all three age groups. These data are very challenging and suggest the need for similar surveys to be made under carefully controlled conditions between areas with very low fluoride levels and other areas with water-borne fluoride levels that are optimal for achieving the maximal dental benefits consistent with insignificant endemic enamel fluorosis.

DIETARY RELATIONSHIPS OF FOOD TO ORAL DISEASE

Relationships of diet to oral problems are of major importance, since our foods are the major sources of the nutrients necessary for the metabolism of those microorganisms responsible for dental caries and some

forms of periodontal disease. Experimental rodents maintained in germ-free environments do not develop carious lesions or an active periodontal syndrome when fed diets capable of supporting the initiation and development of these oral diseases in the presence of a typical microbial population.[24] Likewise, the introduction of a caries-producing diet by tube directly into the stomach of rats prone to develop carious lesions, and with the caries-producing oral flora, results in the prevention of dental caries.[16] The same test has not been made for periodontal disease.

Human populations for many centuries have had the problem of dental caries. However, the prevalence and the rate of progression of lesions have increased greatly in recent centuries and especially in the last century. This trend has been closely associated with changing food usage and especially with the availability and the use of refined flours and sugars. In animal populations dental caries do not occur when carbohydrate-free diets are fed.[28] Oral ingestion of sucrose alone, when the rest of the diet is tube fed, causes caries.[13] While efforts to rank the caries-producing abilities of individual carbohydrates vary from one assay system to another in dependence upon the species of rodent used, the microbial flora and the type of carious lesion observed (lesions in the pits and fissures vs. those on the smooth surfaces), the monosaccharides and disaccharides in general are capable of supporting much more rapid initiation and development of carious lesions than the starches. In some investigative situations, sucrose (table sugar, primary sweetening agent in commerce) is more cariogenic than other monosaccharides and disaccharides.[6, 11, 17] In other assay procedures, sucrose is not uniquely cariogenic in comparison with other monosaccharides and disaccharides.[30] In laboratory evaluations sucrose is the most readily utilized substrate for the formation of dextrans by cariogenic Streptococci. Dextrans are polymers of glucose and currently are believed by some investigators to be of primary importance for the establishment of plaque on the tooth surfaces which acts as a tenaciously adherent nidus for further proliferation of bacteria and for the elaboration of metabolic by-products capable of initiating carious lesions. Some mechanism and material of the characteristics of the dextrans would be especially helpful in the establishment of lesions on the smooth surfaces of the teeth. However, in the pits and fissures of the occlusal surfaces and on the proximal surfaces between teeth, microorganisms and food can be retained without such adhesive residues. Sucrose is not the only substrate for the formation of dextrans; in at least one experimental situation, other monosaccharides and disaccharides caused carious lesions on the smooth surfaces of rat molars and promoted the formation of small amounts of dextrans in mixed bacterial cultures.[30]

Sucrose currently is the primary sugar in the human dietary. While its complete replacement in the human dietary would be difficult because of the many desirable characteristics of sucrose in palatability and ease of industrial utilization in food preparation, the data from laboratory experiments suggest that complete replacement of sucrose by other monosaccharides or disaccharides would not necessarily result in major reductions in the incidence of dental caries, except possibly on the smooth surfaces. At best, the reductions in incidence of dental caries

would likely be temporary, and a return to the current high levels would occur as microorganisms adapted metabolically to the new sugars.

The starches in all laboratory evaluations have proven to have a lower ability to initiate and support the development of carious lesions. Some variation exists between starches with respect to their cariogenic ability.[11] Starches are more cariogenic in some strains of laboratory animals than in other strains; this observation suggests the likelihood of different eating patterns, different oral clearances, different microbial flora, or some combination of these parameters among different strains. These same parameters may be present in human populations and contribute toward the differences in caries susceptibility among individuals and among populations.

Numerous human trials to evaluate the role of the inclusion of sugar, candy, or other confectionary items in the diet have been conducted over the past several decades. The likelihood is high that not one of these trials has been flawless in design or execution. Undoubtedly this type of evaluation is extremely difficult to control because of the length of time needed for adequate clinical evaluation of new carious lesions, and the problems of boredom with the particular test material provided or of bootlegging the material from the experimental group to the controls, etc. However, the data very consistently reveal that increased amounts of candy result in increased incidences of dental caries. Sometimes the increase is quite small, but on other occasions quite large. The clinical evaluation considered by many people to be most authoritative was conducted in Vipeholm, Sweden, with young adults in a mental institution.[12] This study has been criticized because young adults were used rather than children, who have a higher caries susceptibility and more available surfaces to decay, and also because the data were reported in terms of new carious teeth rather than per cent of available caries-free surfaces. These criticisms have validity; however, the results are strongly suggestive that sucrose in solution or in bread, that is, in forms which are rapidly cleared from the oral cavity, had relatively little influence on the incidence of caries, whereas comparable or lower amounts of sucrose in materials which are readily retained on tooth surfaces (such as toffees, caramels, or chocolate) caused increases in the incidence of caries. Chocolate appeared to have a lesser effect than the other candies. In addition, the use of any form of sucrose at meals had less effect on caries incidence, in comparison with a major influence when fed between meals.

Numerous investigators over the years have speculated about the presence of natural inhibitors in foods which may be lost during the refining process.[14] There are suggestions of this from epidemiological surveys.[8] Usually other variables exist which could equally well explain the observed differences. Some additional information from in vitro experiments in which natural foods have been incorporated into culture media and from some animal assays support the possibility of the existence of natural caries inhibitors in food.

The supplementation of caries-producing diets for rodents with relatively high levels of phosphates has been of intense interest in recent years. Various phosphates have been evaluated.[23] Tricalcium ortho-

phosphate and dicalcium orthophosphate had little or no effect in preventing caries. Sodium and potassium hydrogen orthophosphate were highly effective. The most effective of the inorganic phosphates has been sodium trimetaphosphate. An organic phosphate, sodium phytate, has also been highly effective. The latter compound is of interest in relation to the possibility of natural inhibitors in foods, since the phytates occur in fairly high amounts in the bran of cereal grains. Bran is now used primarily in animal feeds, whereas before the taste preferences for a highly refined white flour, it was a routine component of the human diet.

Phosphate supplementation of human diets has proven to be discouraging as a means of caries prevention. In the earliest study in Sweden, 2 per cent dicalcium orthophosphate additions to soft bread, hard bread, wheat flour used in cooking, and sugar in the school lunch program were reported to result in a 50 per cent reduction in the first year and a 40 per cent reduction in the second year.[35] Caries examination was limited to the four proximal surfaces of the maxillary incisors. Fluoride concentration in the phosphate averaged 250 ppm in the first year but only 20 to 25 ppm in the second year. Two other evaluations of the influence of the same chemical form of phosphate as a supplement to the flour or to the flour and sugar in residential schools resulted in insignificant differences.[2, 31] The reason for the difference between the original and the latter trials is not known. In any case, the likelihood of a consistent benefit from the use of dicalcium orthophosphate was not high in view of its small effect in animal population in contrast to several other fluorides. Dicalcium orthophosphate was used to maintain the total calcium-phosphorus ratio of the diet near 1.0 because of the concern that a major shift below 1.0 by the addition of major amounts of a sodium or potassium phosphate might be deleterious to the health of the subjects. In all probability, undue concern was expressed about the calcium-phosphorus ratio and more meaningful experiments could have been conducted with a phosphate judged to be the most beneficial from rodent experiments. The same kind of clinical trials needs to be repeated with supplementation by sodium trimetaphosphate or sodium phytate of the flour and sugar used in a residential school or schools. Particular care should be taken in future trials to use child populations in which newly erupting teeth are present. The data for these teeth should be tabulated separately from that for previously erupted teeth.

Recently, breakfast cereals supplemented with a mixture of sodium monohydrogen and dihydrogen phosphates have been compared with unsupplemented cereals. Children in the study were examined by two different examiners.[34] The results from both examiners indicated significant reductions in dental caries as a result of the use of the phosphate-supplemented cereals. However, the reduction was much greater for one examiner than the other. In two additional studies, significant reductions were reported.[1, 7] In a similar study with phosphate-supplemented breakfast cereals, no reduction was observed.[25] One major problem with the use of a phosphate carrier which is not likely to be eaten more than once daily is the low level of phosphate provided and its infrequent presence in the oral cavity. These striking differences from the situation in animal

assays could explain the dissimilar results from human to animal trials. This area is an extremely interesting one, which needs continued investigation.

SUMMARY

Nutritional recommendations for optimal oral health are in general the same as for other areas of the body, and differ only through the need to include and emphasize some additional facets. The daily consumption of a well chosen, varied selection from the four basic food groups is the keystone of the nutritious diet for oral health as well as for general health. When individual caloric needs require additional servings beyond the amounts recommended from these major food groups, optimal oral health will be achieved by the use of foods which are readily cleared from the mouth and which contain low amounts of readily fermentable carbohydrates. Eating between meals should be discouraged; when snacks are consumed, they should consist of fruits and vegetables rather than candy, cookies, sweet rolls, etc. Good oral hygiene procedures after food consumption are highly important in the maintenance of oral health, as are periodic dental examinations.

In addition to these recommendations, which are largely concerned with the development and maintenance of the soft tissues and the maintenance of the teeth and their supporting structures, the provision of adequate amounts of fluoride during the development of the teeth leads to the formation of teeth which are much less subject to rapidly progressing carious lesions after eruption into the oral cavity. Where communal water supplies are available, the introduction of an appropriate amount of fluoride is extremely effective, inexpensive, and safe. In the absence of communally fluoridated water, an appropriate proprietary source of fluoride should be used throughout tooth development.

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Alcoholism, Drug Addiction, and Nutrition

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Alcoholism and drug addiction are major causes of malnutrition among peoples to whom adequate food is available. Nutritional deficiency in these instances is due largely to lack of proper food intake because of inhibition of central mechanisms which control appetite and hunger. In addition, adaptive or toxic responses to ethanol, barbiturates, or narcotics may contribute to malnutrition by interfering with absorption or utilization of ingested nutrients. Nutrient depletion may lead to central nervous system and liver damage, the clinical manifestations of which may help perpetuate alcoholism and drug addiction. This article (1) considers the effect of alcoholic beverages and addictive drugs on intermediary metabolism and nutrient balance, and (2) outlines the role of nutritional therapy in rehabilitation of the alcoholic and the drug addict.

INTERMEDIARY METABOLISM

Metabolism of drugs occurs principally in the liver in conjunction with the processing of foodstuffs and endogenous metabolites. Micro-

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somal enzymes are responsible for conjugation, detoxification, and oxidation of a given drug. Stimulation of this mechanism which is controlled by DNA-dependent RNA synthetic processes[8] accelerates the rate of removal and decreases drug activity or toxicity.[6] When a drug is given repetitively, greater amounts are required to produce the same effects because of these adaptive reactions, which also occur in the brain and other tissues. It has been suggested that these processes which lead to tolerance and dependence involve alterations in serotonin turnover, immunologic-like reactions, and other biochemical and physical changes. Protein, vitamin, or mineral depletion, by interfering with the production of essential enzymes and substrates, may either increase or decrease tolerance or toxicity.[16]

Ethanol

Metabolism of alcohol depends upon ethanol-oxidizing enzymes whose activity is reduced by a deficiency of protein, nucleogenic vitamins, or zinc.[11] The alcohol dehydrogenase-NAD complex is largely responsible for oxidation of ethanol[3] (Fig. 1); catalase, NADP oxidase,[2] and microsomal oxidase[22] are contributory. Inhibitors such as pyrazole,[19] puromycin, and actinomycin[14] have each been found to reduce ethanol-oxidizing enzymes and removal capacity. A similar effect has been noted in experimental protein and folate deficiency,[11] but not in riboflavin deficiency.[3] Ethanol tolerance may improve with the correction of overt malnutrition; however, many malnourished alcoholics exhibit normal or increased alcohol removal capacity.

Oxidation of ethanol evokes adaptive subcellular structural changes, including hypertrophy of the endoplasmic reticulum and enlargement of mitochondria.[22] Identical changes have been noted in diet-induced protein depletion. These abnormalities are diminished, however, when ethanol is given in the presence of high protein intake or with simultaneous administration of androgenic-anabolic steroids. Hyperplasia of

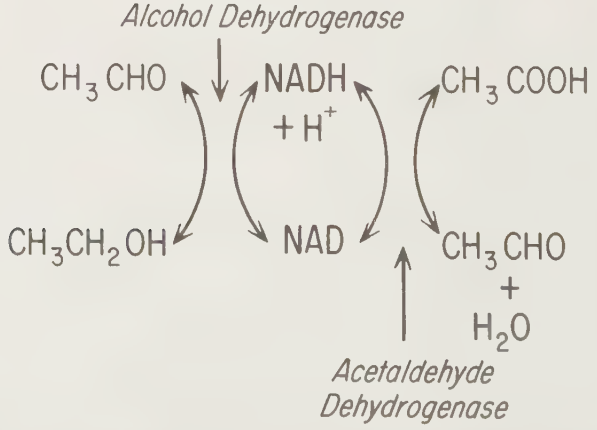

Figure 1. Enzymes and cofactors involved in the major pathway for oxidation of ethanol. Alternatively, catalase and TPNH oxidase may catalyze ethanol metabolism.

the smooth endoplasmic reticulum is usually accompanied by an increase in microsomal enzymes (Fig. 2), thus facilitating oxidation of ethanol and other drugs.[22] Many alcoholics are able to ingest 1 pint to 1 quart of ethanol daily without significant ill effect. Such subjects usually exhibit an increase in ethanol-oxidizing enzymes. Increases in enzymes occur only as long as nutrient precursors are available, so that depletion of essential nutrients may lead to a hypertrophic hypofunctioning smooth endoplasmic reticulum.[17] It has been found that alcoholics who fail to eat properly exhibit reduced ethanol tolerance and are more susceptible to tissue injury.[11]

Barbiturates

Barbiturates also adaptively produce hypertrophy of the smooth endoplasmic reticulum, with an increase in drug tolerance which requires progressively larger doses to achieve the same cerebral effects. Ethanol added on an in vitro basis to liver slices inhibits pentobarbital hydroxylase activity; it has been suggested that this may account for marked sensorial depression which occurs after receipt of ethanol and barbiturates.[21] In vivo studies show that ethanol rapidly increases pentobarbital hydroxylase activity (Fig. 2), so that the observed clinical response probably represents synergistic effects of these agents in the brain, rather than an alteration of removal capacity.[24] Barbiturates may be better tolerated in alcoholics without tissue injury, but often produce greater somnolence in patients with overt brain, liver, or renal damage attendant to chronic alcoholism and malnutrition.

Narcotics

Unlike ethanol and barbiturates, narcotics have not been found to produce gross structural and functional changes, although clinical adaptive reactions to narcotics are much more intense and longer in duration. Excretory pattern and tissue distribution of radioactive morphine is identical in normal and tolerant animals.[18] Occupation and inhibition of receptor sites may account for response to antidotes, logarithmic dose-response curves, and cross tolerance, but fails to explain persistence of tolerance for long periods after the drug is stopped.[1] It has been postulated that a narcotic such as morphine may inhibit the action or synthesis of a neurohormone, thereby causing depression, sedation, and analgesia, and that it may also depress production of the neurohormone synthesizing enzyme, thereby increasing the amount of morphine needed to depress the central nervous system.[23] This thesis is consistent with the finding that morphine administration depletes brain catecholamine[26] and increases turnover of serotonin,[26] and could explain the blocking effects of cycloheximide, a potent inhibitor of protein synthesis on tolerance and physical dependence.[1]

NUTRIENT BALANCE

Alcoholics are often overweight during the early phase of their disease, when calories from alcoholic beverages are added to those

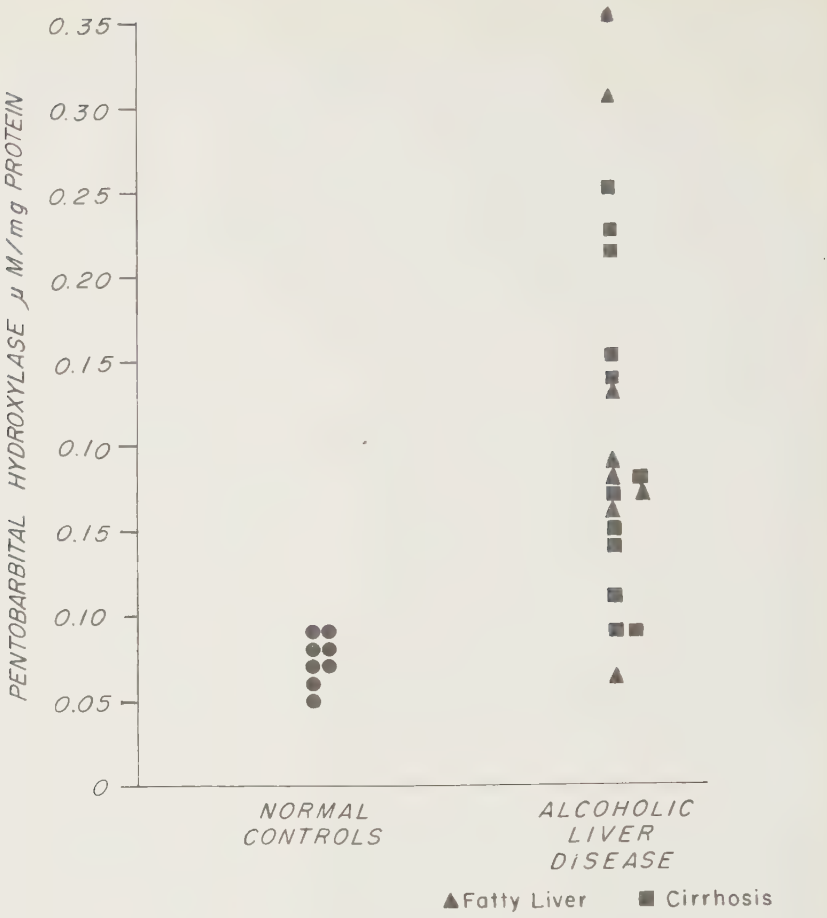

Figure 2. Microsomal pentobarbital hydroxylase activity in control and alcoholic subjects.

provided in a normal diet. In addition, ingestion of alcoholic beverages without food often leads to low-grade hypoglycemia which stimulates hypothalamic centers regulating appetite. As the amount of ethanol intake increases, there is a concomitant reduction in food intake with weight loss equivalent to that achieved when one takes barbiturates, narcotics, or amphetamine. The reduced appetite is due to the "stimulation" or euphoria produced by these drugs. Administration of such drugs to patients with frontal lobotomy does not alter their appetite, suggesting that anorexia is due to cortical effects of these agents.

Nutrient Intake and Absorption

Loss of appetite and the eating of selected foods lead to varying degrees of malnutrition. Clinical and laboratory evidence of nutrient deficiency occurs in the majority of alcoholics and addicts whose intake of ethanol or drugs interferes with work and social responsibilities on a

continuing basis. Dietary patterns in these subjects are determined by economic status, geographical location, religious indoctrination, and ethnic background. Dietary inadequacy has been encountered in each of over 3500 alcoholics and addicts admitted to two large municipal hospitals and a Veterans Administration Hospital because of medical complications.

Absorption abnormalities are common in alcoholics or drug addicts because of the high incidence of lesions of the intestine, liver, and pancreas. Intestinal dysfunction or mucosal damage may result from drug toxicity, protein deficiency, or both. It leads to reduced intestinal transport of dietary fats, calcium, magnesium, and vitamins.[9] Similar absorptive defects occur in subjects with liver disease and pancreatic disease which alter bile and pancreatic secretion, respectively.

Nutrient Utilization

Malutilization of ingested micronutrients is common in both the alcoholic and the drug addict because of the frequent presence of liver disease. Acute phases of liver injury induced by ethanol and the virus of hepatitis are both characterized by decreased ability to convert available nutrients into metabolically active forms. The resulting imbalance may interfere with nucleic acid synthesis, thereby further altering the utilization of nutrients for energy transformation by mitochondria, and for synthesis and degradative processes by microsomes or lysosomes. Clinical evidence of this phenomenon has been documented in patients with Wernicke's encephalopathy in whom thiamine malutilization was due to associated folic acid and vitamin B_{12} deficiency.[5]

Effects of Nutrient Depletion

Nutrient deficiency leads to a variety of symptoms. It may be responsible for asthenia, weakness, anxiety, and other vague complaints often present in the alcoholic or drug addict. Of particular importance is the suggestion that a deficiency of vitamins or minerals may contribute to mental aberrations which help perpetuate alcoholism and drug addiction. Pauling has postulated that cerebral avitaminosis without overall body depletion may cause mental dysfunction.[20] Investigations were undertaken to assess the applicability of this postulate to neuropsychiatric syndromes attributed to thiamine deficiency. Results indicate that thiamine in the cerebrospinal fluid is reduced only when there is total body depletion, but that subclinical deficits may occur without classical clinical features such as neuropathy.[25] It is, therefore, necessary to utilize sensitive laboratory techniques to detect subclinical deficiency states.

Mental changes precipitated by the withdrawal of alcohol or drugs are not currently believed to be due to nutrient deficits. Characteristically, such patients have an increase in spinal fluid lactate and pyruvate, attributable to anerobic glycolysis (Fig. 3).[13] Occasionally, dramatic decrease in hyperkinesis, hallucinations, and other manifestations of withdrawal occurs in patients after parenteral administration of magnesium, thiamine, nicotinic acid, or vitamin B_6. In these instances,

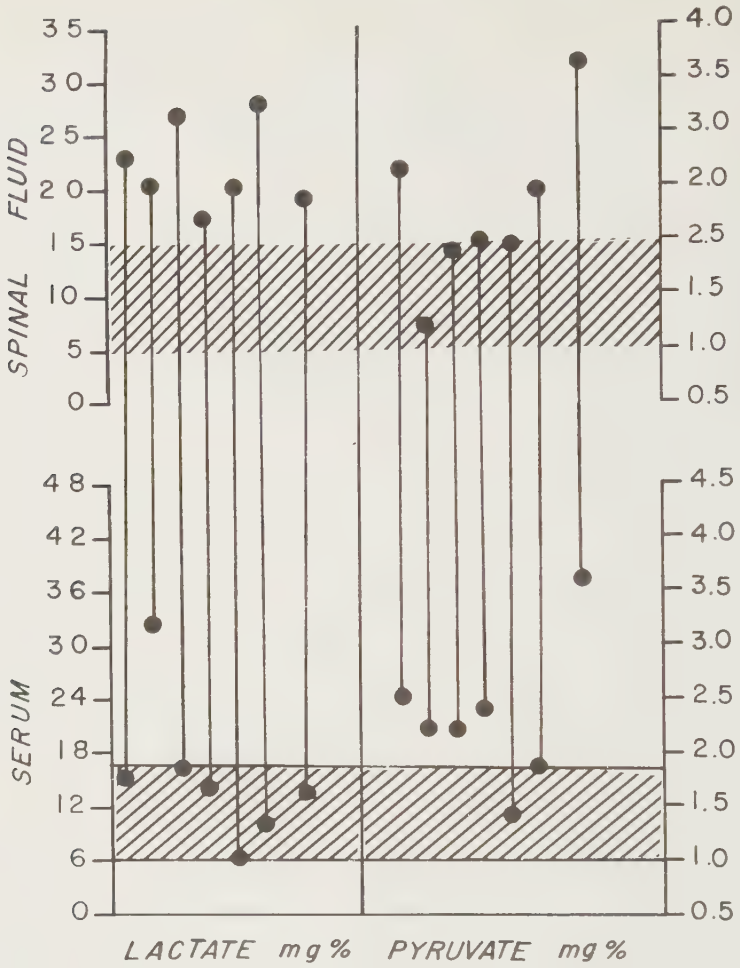

Figure 3. Relationship of serum and spinal fluid lactate and pyruvate in delirium tremens.

a deficiency of these micronutrients may contribute to withdrawal phenomena by interfering with cerebral glycolysis.

Peripheral neuritis is common in the alcoholic and is sometimes present in the chronic drug addict. It is usually due to thiamine depletion, although a deficiency of vitamin B_6, pantothenic acid, or nicotinic acid may produce identical signs.[7] Wernicke's encephalopathy is seen primarily in alcoholics but may also occur in drug addicts. Convulsive seizures are seen in both alcoholics and drug addicts, and may be precipitated by hypoglycemia, vitamin B_6 deficiency, thiamine depletion, or magnesium deficiency.

The liver is the other major organ system subject to injury because of nutrient deficiency attendant on alcoholism and drug addiction. Liver injury in the alcoholic results from a combination of nutritional de-

ficiency, ethanol toxicity, and constitutional factors,[10] whereas, in the drug addict, it is usually due to the hepatitis virus. In both instances, the necrotic cells release essential micronutrients, so that extra protein, vitamins, and minerals should be provided for tissue repair. Failure to supply adequate nutrients leads to progressive cell damage. Each of 26 malnourished alcoholics with steatonecrosis who continued to consume ethanol and eat poorly developed cirrhosis after a 2 to 8 year period.[12] In alcoholics nutrient imbalance also contributes to complications of cirrhosis such as ascites, anemia, a bleeding tendency, mental changes, and hypogonadism.

Recognition of Nutrient Deficiency

Evidence of weight loss or clinical stigmata of vitamin deficiency are suggestive signs of malnutrition in the alcoholic or drug addict. Glossitis represents the most readily recognized clinical sign of nutritional deficiency in such patients;[15] the status of filiform and fungiform papillae should, therefore, receive special attention on physical examination. Isolated deficits of protein, iron, nicotinic acid, riboflavin, folic acid, vitamin B_6, vitamin B_{12}, or biotin may each produce this sign, which also occurs in patients with dentures in the absence of nutrient depletion. A therapeutic trial of vitamins is indicated in patients with glossitis, with or without prior laboratory confirmation. It is now possible to measure circulating levels of each of the B-complex vitamins so that vitamin therapy can be monitored.[1] Simultaneous measurement of blood thiamine and red blood cell transketolase, blood nicotinic acid and red blood cell pyridine nucleotides, and blood B_6 and transaminase before and after treatment permits recognition of abnormal vitamin assimilation.

NUTRITIONAL THERAPY IN REHABILITATION

Intensive in-hospital diet therapy is desirable to repair overt tissue injury in the malnourished alcoholic or drug addict. Parenteral therapy should be used to correct fluid and electrolyte imbalance, vitamin depletion, and hypoglycemia in acutely ill patients with withdrawal syndromes. A nutritious diet with appropriate supplements should be provided subsequently. The diet should contain sufficient calories; frequent, small appetizing feedings are desirable for those who are chronically ill or depressed.

A program of continuous nutritional therapy should supplement attempts to interrupt alcoholism and drug addiction. Development of regular mealtimes is helpful in the ambulatory patient, since this contributes to family cohesiveness and diminishes psychological and social difficulty. Special arrangements are needed to provide proper post-hospitalization dietary treatment for the indigent alcoholic or addict. Organization of group programs which include eating together is particularly valuable in this group of patients. Alcoholics and drug addicts who are refractory to attempts at rehabilitation should be encouraged

to eat properly in order to reduce complications attendant to nutritional deficits. Overnutrition should be avoided. There is no virtue in parenteral administration of vitamin or mineral supplements in the absence of a deficiency state. This practice—which is common in urban communities—should be discouraged, because these materials are usually rapidly excreted and exert no known effect on the desire for alcohol or drugs, and because such regimens replace false emphasis on the role of nutrition in prevention or treatment of alcoholism and drug addiction.

SUMMARY AND CONCLUSIONS

Malnutrition is frequent among alcoholics and drug addicts because of failure to ingest an adequate diet. This is initially due to inhibition of appetite by cerebral effects of ethanol and addictive drugs, but may subsequently occur as a result of tissue injury which alters absorption and utilization of essential nutrients. Nutrient deficiency may (1) alter the metabolism of ethanol, barbiturates, and narcotics; (2) modify reaction patterns to these drugs; and (3) contribute to the development of neuropsychiatric syndromes, peripheral neuropathy, and liver disease commonly associated with alcoholism and drug addiction. Provision of excess nutrients exerts no known effect per se on the desire for alcohol or drugs.

It is essential to recognize and correct nutritional deficits in any rehabilitation program for alcoholics and drug addicts. Parenteral therapy is necessary to correct fluid, mineral, and vitamin deficits in acutely ill patients with withdrawal syndromes; a nutritious diet with appropriate supplements is desirable for repair of chronic tissue injury. Development of a pattern of regular mealtimes is an important part of an ambulatory regimen for control of alcoholism, drug addiction, and their medical complications.

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Diet Therapy of Diabetes Mellitus

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The role of diet therapy in the management of diabetes is a most important one. A juvenile diabetic patient cannot be controlled with insulin alone, and management would be impossible without certain dietary restrictions. However, large numbers of maturity onset diabetic patients may be well managed by dietary control alone. The philosophy of diet prescriptions in diabetes mellitus has been changing from the hard line of many years past to one in which the diet conforms to that of the rest of the family group. Restrictions are at a minimum in those who are not obese and have had reasonable eating habits prior to the development of diabetes mellitus. The weighing of food on scales has given way to the measured diet, utilizing ordinary household measuring devices. However, the totally free diet is not an acceptable alternative.

OBJECTIVES

During childhood there must be sufficient caloric intake to insure adequate nutrition and normal gain in weight and height with good activity potential. Obese adults must lose weight, while normal weight adults must maintain their weight and not fatigue easily. The weight gain of the pregnant diabetic female must be carefully controlled. In general, diet should aim to: (1) normalize the existing dysmetabolism and (2) normalize body weight. Overnutrition should be avoided. Obesity is the bane of diabetics! A maturity onset diabetic should be made to understand that adequate weight reduction may be the only treatment necessary for him, and might also reduce the likelihood of his developing some of the more serious vascular complications of diabetes mellitus.

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The diet must also (3) be readily accepted and vary as little as possible from the diet of others in the family constellation; (4) be adapted to the patient's way of life, be it sedentary or strenuous; (5) improve the patient's feeling of well-being.

REQUIREMENTS OF THE DIABETIC DIET

Total Calories

Patient-related Factors

1. Age: childhood, adolescent, mature adult, or geriatric patient.

2. Weight: Is there a difference between the ideal and actual body weight? In the obese patient a low calorie diet (1000 to 1500 calories) may be advised. The underweight patient will receive a high caloric diet daily.

3. Physiological situation: pregnancy, lactation, and growth all increase the caloric requirement.

4. Activity: The diet will be related to different conditions of activity. Sedentary adults with weight within 10 per cent of the "ideal" require 30 calories per kg. per day. With moderate activity, 35 calories per kg. are necessary, and marked activity requires 40 calories per kg. Patients at bed rest might do well on only 20 calories per kg.

When treatment has been stabilized, the dietary requirements of a diabetic patient are identical to those of the nondiabetic patient. An obese diabetic patient with a healthy appetite should receive a diet high in bulk content; consequently the gram to calorie ratio should be high in this type of patient, but low in an underweight diabetic patient who requires additional calories rather than bulk.

Children's Diets. Children's diets are based upon age and nutrition. We prescribe a diet of 1000 calories for a child 1 year of age, and add an additional 100 calories for each year of growth. Thus a 1 year old child receives 1000 calories, a 5 year old child receives 1400 calories, and a 10 year old receives 1900 calories. If a child is obese we subtract several hundred calories from the daily diet. If the child is underweight, we add an additional several hundred calories. In children, adequate provision must be made for growth and the activity and mainten-

Table 1. *Caloric Requirement of Adults Related to Activity*

	CALORIES PER KILOGRAM PER DAY			
	MARKED ACTIVITY	MODERATE ACTIVITY	SEDENTARY	BED REST
Underweight (< 20 per cent of ideal weight)	45–50	40	35	20–25
Ideal weight	40	35	30	15–20
Overweight (> 20 per cent of ideal weight)	35	30	15–20	15

ance of reasonable body weight. During peak growth periods, adolescent girls require 2400 to 2700 and adolescent boys 3100 to 3600 calories per day.

In the obstetrical patient, the objective in management is weight control, and according to White, 30 calories per kg. of ideal body weight will suffice for the 12 lb. gain.[10]

Partition of Calories

The normal American diet usually consists of 50 per cent carbohydrate, 35 per cent fat, and 15 per cent protein. For the purpose of simplification, this is easily changed to 40 per cent carbohydrate, 40 per cent fat, and 20 per cent protein.[11] One fifth of the total calories is given for breakfast, two fifths for lunch, and two fifths for dinner. From the total daily calories which have been calculated, three 15 to 20 gram snacks are subtracted and offered mid-morning, mid-afternoon, and at bedtime. Highly concentrated carbohydrates such as candy, syrup, icing on cakes, jelly, and pastries are avoided. This method avoids large fluctuations of blood glucose.

Carbohydrates. The quantity of carbohydrate per day allowed for adult diabetics varies between 150 and 300 grams. Diets calculated to contain less than 100 grams of carbohydrate are unappealing and might result in ketosis. Their preparation would severely test the ability of the most competent dietician. When caloric restriction is required, the amount of protein may be decreased to allow for additional carbohydrate. Slowly absorbed carbohydrates are selected, rather than the concentrated type.

The amount of carbohydrate necessary in the daily diet is easily calculated by dividing the total daily caloric requirement by 10; for example, a 10 year old child who requires 1900 calories needs 190 gm. of carbohydrate per day.[4] A 70 kg. adult who has a sedentary occupation will require 2100 calories per day (70 kg. $\times$ 30 calories per kg.). The 2100 divided by 10, gives 210 gm. of carbohydrate per day, approximately 40 per cent of the total daily calories. Amounts of carbohydrate greater than 300 gm. per day may be too much for the metabolic capacity of the diabetic, and may result in a great loss of glucose in the urine.

Protein. Children below 3 years of age require 2.5 gm. of protein per kg. of body weight; older children require 2 gm. per kg. per day. The recommended allowance of protein for healthy adults is 1 gm. per kg. of body weight.[8, 9] The diabetic patient may require extra protein in the diet to counteract losses from gluconeogenesis and nephropathy. In these instances, additional protein, up to 0.5 gram per kg. per day, should be added to the diet. Pregnancy and debilitating disease also require additional protein, whereas uremia and hepatic coma usually dictate decreased amounts of protein. A simple way of calculating the amount of protein required is to divide the carbohydrate requirement (in grams) in half. The result will be the required number of grams of protein per day, which approximates 20 per cent of the total calories.

Fat. Although the serum cholesterol levels may not always reflect the level of other lipids, it is the major component of vascular atheromas

in patients with elevated serum lipids. With elevated serum lipids, low fat diets (containing less than 30 per cent of the daily calories) are difficult to calculate, very unpalatable, and consequently unjustified. The general consensus of opinion as of this date favors the use of diets high in polyunsaturated fats which will result in normal serum levels of cholesterol, triglycerides, free fatty acids, and lipoproteins.[1, 3, 5, 6] Animal fats are to be limited, as are high cholesterol containing foods. Fish and poultry are most desirable. Saturated fats should be markedly restricted, but mono-unsaturated fat may be freely used.[2] Diets utilizing larger amounts of polyunsaturated fats have been found to significantly decrease serum cholesterol and other lipids. Many believe that diets containing low cholesterol and high polyunsaturated fat are useful in the treatment and prevention of the angiopathies of diabetes.[5, 7]

The grams of fat in the diet are calculated exactly as is the protein content (the grams of carbohydrate per day divided in half), the result being the number of grams of fat required, which approximates 40 per cent of the total calories.

VITAMINS AND MINERALS. The diabetic diet to be outlined contains sufficient vitamins and minerals. Diabetics who are poorly controlled, or those with infections or acidosis may require vitamin supplementation. If there is doubt regarding the patient's consumption of the prescribed diet, a multivitamin preparation should be advised.

ALCOHOL. Alcohol may be added to the diabetic diet provided that the intake is small and that the relatively high caloric value of alcohol is considered in the formulation of the diet.[9] One gram of alcohol provides 7 calories. One gram of carbohydrate and 1 gram of protein each provide 4 calories, 1 gram of fat provides 9 calories.

EXAMPLES

Male

Ideal Weight, 150 lb.
Actual Weight, 154 lb. (70 kg.)
Activity, marked
70 kg. × 40 cal. = 2800 calories

$$\frac{2800}{10} = 280 \text{ gm. carbohydrate}$$

$$\frac{280}{2} = 140 \text{ gm. fat}$$

$$\frac{280}{2} = 140 \text{ gm. protein}$$

Female

Ideal weight, 108 lb.
Actual weight, 110 lb. (50 kg.)
Activity, sedentary
50 kg. × 30 cal. = 1500 calories

$$\frac{1500}{10} = 150 \text{ gm. carbohydrate}$$

$$\frac{150}{2} = 75 \text{ gm. fat}$$

$$\frac{150}{2} = 75 \text{ gm. protein}$$

CONVERSION OF THE DIABETIC DIET PRESCRIPTION INTO MEALS

Of primary importance in the preparation of diabetic diets are the dietary habits and food preferences of the individual—his religious and ethnic group, and his social and economic status. The diet to be described here is the one approved by the American Diabetes Association, the exchange diet. This diet is measured with gross household measures—cups, slices, tablespoons—and is neither rigid nor weighed. Deviations in amounts occurring sporadically are not significant.

Explanation of the Diet to the Patient

In making up your diet plan, which is based upon your own particular needs, we selected foods from six basic types: vegetables, fruit, bread, meat, fat, and milk.

This diet allows you to select from a wide variety of foods in each group. For example, instead of one serving of bread you may select one serving of any of the foods shown in List 2. In addition, this diet allows you to measure rather than weigh food. In this way you can maintain your proper food intake just as easily when you are away from home.

Do not add or omit any food servings. In other words, eat the exact amount and kinds of foods prescribed by your doctor.

This plan is easy to follow. The foods listed are available everywhere. In most cases they are the same as for individuals without diabetes. Your meals will be varied and appetizing and, above all, will help you to maintain a desirable weight, feel well, and control your diabetes.

General Rules

1. Food Measuring: *The food you eat must be measured.* Get a standard 8-ounce measuring cup, a measuring teaspoon, and tablespoon. Be sure that your measurements are level, and remember that most foods are measured after cooking.

2. Preparing your food: Meats and fish should be baked, boiled, or broiled. Do not fry your food unless you use the amount of fat you are allowed in your meal. Your vegetables may be prepared with those for other members of your family, but your share should be removed before extra fat or flour is added.

3. Avoid these foods: Sugar, candy, honey, jam, jelly, marmalade, syrups, pie, cake (except plain sponge cake allowed in your diet), cookies, pastries, condensed milk (containing added sugar), soft drinks, candy-coated gum, fried, scalloped, or creamed foods, beer, wine, or other alcoholic beverages.

4. You may exchange one bread-type of food for another bread-type of food, but not for anything else (you may not exchange bread for meat or for fruits).

5. Only diet soft drinks are allowed.

6. Saccharin should be added to cooked food only after the food has cooled somewhat.

For each meal simply eat the number of servings written by your doctor in the box beside each food list (see p. 1584-1585).

List 1. Vegetables—carbohydrates, 7 gm.; protein, 2 gm.; calories, 36.

Amount: 1 cupful

Asparagus	Broccoli*
Brussels sprouts*	Cabbage
Cauliflower	Cucumber
Eggplant	Beet greens
Chard	Collards
Dandelion	Kale
Poke	Spinach
Turnip, greens	Mushrooms
Okra	Romaine
Rhubarb (without sugar)	Sauerkraut
String beans (young cooked)	Squash (summer)
Tomatoes (cooked)	

Amount: ½ cup

Beets	Carrots
Onions	Peas, green
Pumpkin	Rutabagas
Squash, winter*	Turnips

List 2. Breads, vegetables, and ice cream—carbohydrate, 15 gm.; protein, 2 gm.; calories, 68.

Bread, 1 slice
Biscuit, roll, 1 (2 in. diam.)
Muffin, 1 (2 in. diam.)
Cornbread, 1½ in. cube
Flour, 2½ tbsp.
Cereal, cooked, ½ cup
Cereal, dry (flakes or puffed), ¾ cup
Rice or grits, cooked, ½ cup
Spaghetti, noodles, etc., ½ cup
Crackers, graham (2)
Crackers, oyster, 20 (½ cup)
Crackers, saltine (5)
Crackers, soda (3)
Crackers, round (6 to 8)

*These vegetables have a high vitamin A content; at least one serving a day should be used.

List 2. (Continued)

Vegetables
Beans (lima, soy, etc.), dry, cooked, 1/2 cup
Peas (split peas, etc.), dry, cooked, 1/2 cup
Baked beans, no pork, 1/4 cup
Corn, 1/3 cup
Parsnips, 2/3 cup
Potatoes, sweet, or yams, 1/4 cup
Potatoes, white, baked or boiled, 1 (2 in. diam.)
Potatoes, white, mashed, 1/2 cup
Sponge cake, plain, 1 1/2 in. cube
Ice cream (omit 2 fat servings), 1/2 cup

List 3. Meats—protein, 7 gm.; fat, 5 gm.; calories, 73.

Meat and poultry (beef, lamb, pork, liver, chicken, etc.)
1 slice (3 in. × 2 in. × 1/8 in.)
Cold cuts, 1 slice (4 1/2 sq., 1/8 in. thick)
Frankfurter, 1 (8 to 9 per lb.)
Codfish, halibut, etc., 1 slice (2 in. × 2 in. × 1 in.)
Salmon, tuna, crab, lobster, 1/4 cup
Oyster, shrimp, clams, 5 med.
Sardines, 3 med.
Cheese, cheddar, American, 1 slice (3 1/2 in. × 1 1/2 in. × 1/4 in.)
Cheese, cottage, 1/4 cup
Egg, 1
Peanut Butter, 1 tbsp.

Limit peanut butter to one serving per day unless carbohydrate is allowed for in diet plan.

List 4. Milk—carbohydrate, 12 gm.; protein, 8 gm.; fat, 10 gm.; calories, 170.

Milk, whole, 1 cup
Milk, evaporated, 1/2 cup
Milk, powdered, 1/4 cup
Milk, skim, 1 cup*
Buttermilk, 1 cup*

Add 2 servings from List 6 (Fats) if milk is fat free.

List 5. Fruits—carbohydrates, 10 gm.; calories, 40.

Apple, 1 small (2 in. diam.)
Apricots, fresh, 2 med.
Banana, 1/2 small
Apricots, dried, 4 halves
Berries (blackberries, raspberries, strawberries*), 1 cup
Applesauce, 1/2 cup

*These fruits are rich sources of vitamin C; one serving a day should be used.

Carbohydrate (gm.)	85	91	116	131	131	136	146	161	167	174	199	207	217	254	260	275	283	290	312
Protein (gm.)	53	57	59	61	61	70	70	72	76	85	87	95	95	100	111	120	135	150	154
Fat (gm.)	40	45	45	50	60	65	70	75	80	85	85	90	95	100	115	125	135	150	160
Total Calories	900	1000	1100	1200	1300	1400	1500	1600	1700	1800	1900	2000	2100	2300	2500	2700	2900	3100	3300
BREAKFAST 7 to 8 A.M.																			
List 1 Vegetables	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
List 2 Breads	½	½	½	½	½	½	½	1	1	1	2	2	2	2	2	2	2	2	3
List 3 Meats	½	½	½	½	½	½	½	½	½	1	½	1	1	1	1	1	1	1	2
List 4 Milk	½	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
List 5 Fruits	1	1	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	2
List 6 Fats	–	–	–	1	1	1	1	1	1	1	2	2	2	2	3	3	3	3	3
SNACK Mid-morning 10 A.M.																			
List 1 Vegetables																		–	–
List 2 Breads	½	½	½	½	½	½	½	1	1	1	1	1	1	1	1	1	1½	2	2
List 3 Meats	½	½	½	½	½	½	½	½	½	1	½	1	1	1	1	1	1	2	2
List 4 Milk																		1	1
List 5 Fruits																		–	–
List 6 Fats																		1	2
LUNCH 12 to 1 P.M.																			
List 1 Vegetables	–	–	–	–	–	–	–	–	–	1	1	1	1	1	1	1	1	1	1
List 2 Breads	½	½	½	1	½	1	1	1	1	1	1	1	1	2	2	3	3	3	3
List 3 Meats	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3	4	5	4
List 4 Milk															½	½	½		
List 5 Fruits	1	1	2	2	2	1	2	2	2	1	2	2	2	2	2	2	2	2	2
List 6 Fats	–	–	–	–	1	1	1	2	2	2	1	1	2	3	3	3	3	3	3

SNACK 3 P.M.																			
List 1 Vegetables																		–	–
List 2 Breads	1/2	1/2	1/2	1	1/2	1	1	1	1	1	1	1	1	1	1	1	1	1	1
List 3 Meats																		–	–
List 4 Milk	1/2	1/2	1/2	1/2	1/2	1/2	1/2	1/2	1/2	1/2	1/2	1/2	1/2	1/2	1/2	1/2	1/2	1/2	1/2
List 5 Fruits																		–	–
List 6 Fats																			
DINNER 6 to 7 P.M.																			
List 1 Vegetables	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2
List 2 Breads	–	–			1	1	1	1	1	1	1	1½	1½	3	3	3	3	3	3
List 3 Meats	2	2	2	2	2	3	3	3	3	3	3	3	3	3	4	5	6	6	6
List 4 Milk																			
List 5 Fruits	1	1	1	1	1	1	1	1	1	2	1	1	2	2	2	2	2	2	2
List 6 Fats	–	–	–	–	1	1	2	2	2	2	2	2	2	2	2	3	3	3	4
SNACK Bedtime																			
List 1 Vegetables																		–	–
List 2 Breads	–	–	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
List 3 Meats																		–	–
List 4 Milk	1/2	1/2	1/2	1/2	1/2	1/2	1/2	1/2	1	1	1	1	1	1	1	1	1	1/2	1/2
List 5 Fruits																		–	–
List 6 Fats																		–	–

List 5. (Continued)

Blueberries, ⅔ cup
Cantaloupe, ¼ (6 in. diam.)*
Dates, 2
Figs, dried, 1 large
Grapefruit juice, ½ cup*
Grape juice, ¼ cup
Honeydew melon, ⅛ (7 in. diam.)
Orange juice, ½ cup*
Peach, 1 med.
Pineapple, ½ cup
Plums, 2 med.
Raisins, 2 tbsp.
Watermelon, 1 cup
Cherries, 10 large
Figs, fresh, 1 large
Grapefruit, ½ small*
Grapes, 12
Mango, ½ small
Orange, 1 small*
Papaya, ½ med.
Pear, 1 small
Pineapple juice, ⅓ cup
Prunes, dried, 2
Tangerine, 1 large*

List 6. Fats—fat, 5 gm.; calories, 45.

Butter or margarine, 1 tsp.
Cream, light, sweet or sour, 2 tbsp.
Cream cheese, 1 tbsp.
Mayonnaise, 1 tsp.
Nuts, 6 small
Avocado, ⅛ (4 in. diam.)
Bacon, crisp, 1 slice
Cream, heavy, 1 tbsp.
French dressing, 1 tbsp.
Oil or cooking fat, 1 tsp.
Olives, 5 small

List 7. Foods that need not be measured (insignificant carbohydrate or calories)

Coffee-black
Clear Broth
Lemon
Gelatin (unsweetened)
Mustard (dry)
Saccharin and other noncaloric sweeteners
Pepper and other spices
Low calorie soft drinks
Tea (no cream or sugar)
Bouillon (fat free)
Rennet tablets
Cranberries (unsweetened)
Pickle (unsweetened)
Vinegar
Seasonings

Any amount of the following foods is allowed if eaten *raw:*

Celery
Cucumber
Greens
Lettuce
Collards
Radishes
Tomatoes
Onions
Chicory
Escarole
Mustards
Parsley
Peppers (red or green)
Sauerkraut
Water cress
Ketchup, seasonings

*These fruits are rich sources of vitamin C; one serving a day should be used.

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A Year of Developments in Nutrition and Aging

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Aging and the management of the aged, when viewed in regard to the role of nutrition, are quite different matters. Aging, according to present theory, begins at conception, if not before. As a biological process, it can be altered in a favorable direction during life in utero by careful attention to the health and nutrition of the mother, and in the first two years of life by equally meticulous attention to the health and nutrition of the newborn, the infant, and the young child.

In childhood, adolescence, youth, and maturity, environmental factors, disease, and nutrition have less impact on the genetic patterning which determines the program of aging. Still, by being managed with positive objectives in view, they may assist in deferring chronic disabilities which often are misconstrued as hallmarks of premature aging. The interdiction of smoking, the elimination of accidents, personal and public health measures to combat infectious disease, nutrition to escape the penalties of obesity, atherosclerosis, osteoporosis, and dental caries, and a mental health climate obviating anxiety, alcoholism, drug abuse, depression, and suicide are all contributions which can be applied to defer disability and death even after the genetic die has been cast.

By the time man has aged, his chances of influencing favorably the genetic program by which his biological clock inexorably ticks off his remaining hours are reduced to the vanishing point. His chances of influencing de novo the environmental factors—including accidents, disease, and nutrition—which might diminish his risk of disability are also seriously diminished.

The message is obvious; the challenge is to get it across: The time for concern about old age is during gestation, infancy, and early life. If this concern has not been exercised, no diet, medicine, manipulation, or incantations can undo damage already done. Sadly, too many, while young, boldly assert their disdain for anything but an early demise, only

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to find themselves clinging to life in old age, pathetically espousing any maneuver which promises to wring a few more hours out of the sponge of life. For those who are still young, particularly for those who are in the childbearing and childrearing ages, the chance to listen, to learn, to accept, and to implement a constructive program designed to defer the deleterious effects of premature physiological aging and disability is present – if not for them, at least for their children. For those who are already old, the outlook is more bleak.

This bleakness stems from the fact that there is no evidence that any nutritional regimen is specific for old age per se. Abundant evidence pointing to the virtue of an elite genetic background does exist, but this is small comfort to those whose genetic escutcheon is nonelite. Actuarial statistics strongly support the inference that environmental factors, including accidents, disease, and malnutrition, if prevented, or disease and nutrition, optimally managed, will reduce the disabilities of old age, but this too relieves little anxiety among those who could have taken better care of themselves, had they only known that they would live so long.

The grimness of the scene worsens when the economic and cultural phenomena of today's society cast their shadows on the aged.

Society is youth-oriented; youth is the message of the mass media; youth seduces the news; youth dominates the marketplace; youth saturates the labor market; youth fills available housing; youth absorbs the time of those skilled in the learned professions.

Economically, the aged are among the poorest of the poor. They are unemployable even when their skills are retained. They receive, from pensions, annuities, investments, and social security, scarcely enough to survive, let alone live in comfort, health, and good nutrition.

Culturally, today's technically-developed society has deprived the aged of their place of honor in the extended families of bygone eras. Gone are not only the pleasure, pride, and status of the patriarch, but also the economic and emotional security which the extended family provided.

The aged have met these challenges with certain rational and other irrational measures. They have banded together in organizations whose leaders lobby for more liberal social security benefits, better health facilities, improvements in existing housing, more new housing, and more reasonable food stamp and commodity distribution programs. On the other hand, as individuals, the aged have become the prime benefactors of quacks, nostrum peddlers, and food faddists, simply because they find irresistible the promises held forth by slick promotion artists.

Organizations lobbying on behalf of the aged have not stressed the logic of good nutrition, in part because other issues are more popular with the membership they serve. Since nutrition influences the aging process primarily during youth, the long-range effects of nutrition on the biological processes of aging are rarely recognized among the aged. Since prevention of disability by good nutrition also must begin early in life, lasting effects of nutrition on infirmities already present are rare but not unheard of. The aged who are still mobile represent the elite whose

genetic endowment has characterized, among other things, their nutritional habitus. They feel with some justification that they know how and when and what to eat, and hence are disinterested in approaches directed at the less fortunate non-elite. Since the elite are the leaders of the organized aged, it is not surprising that nutrition is low on the list of priorities of these lobbying groups.

All aged people are the targets of food faddists. The promise of release from disability attracts the non-elite. Even the elite are seduced by hints of possible rejuvenation of strength, beauty, or sexual drive. Since strong belief in the virtue of a given fad may in itself induce short-term benefits, food fad promoters can extract testimonials from some aged persons to lend an aura of credibility to their spurious claims.

The battle to stamp out the food faddists is continuing at what seems to many observers to be a more frenetic but ever less successful pace. Regulatory agencies are hampered by stringent budgets, woefully inadequate personnel ceilings, and court procedures which are so protracted that the defendants have ample time to develop new frauds to replace those which have finally succumbed to the combined efforts of regulatory agencies and the judicial process.

Perhaps the most tragic of all situations among the aged is that in which nutrient deficiencies in the diet contribute to physical disabilities and mental aberrations which lead in turn to unnecessary institutionalization or commitment. Once institutionalized, these unfortunate individuals join a society in which primary malnutrition from improperly designed diets and improperly prepared food, and malnutrition secondary to poor sanitation, inadequate diagnostic efforts, and qualitatively and quantitatively inadequate treatment of disease are prevalent.

The key to preventing the disabilities of premature aging, assisting those already old in making the most of their physical and mental resources, and protecting the aging of all ages from predatory food faddists is effective education.

Members of the Panel on Aging of the White House Conference on Food, Nutrition and Health, meeting in plenary session three times prior to the December, 1969, conference, and in less formal subcommittees many times between July and December, 1969, were unanimous in their recognition of education as the key to the various problems posed by aging. They devoted their deliberations, in large measure, to exploring possible foundations of an effective educational campaign.

It was agreed that the objective of such a campaign should be to persuade every resident of the United States to consume a diet containing the recommended daily allowance of nutrients as proposed by the Food and Nutrition Board of the National Research Council in its most recent revision of recommended daily allowances.

The achievement of this objective requires meaningful education. By meaningful education, the panel referred to education backed up by real materiel—foods, meals, and dining facilities—labeled and staffed in such a way as to complement an educational effort carried out through commercial, nonprofit, and governmental programs, utilizing the most effective methods of communication. Meaningful education needs to

be carried out in a context reinforced by group activities and a positive atmosphere in which social interaction can contribute to the learning process. The development of physical facilities in terms of housing units in the future and in terms of improvement in older housing units is deemed another essential ingredient of the total educational program. Education must also emphasize the interrelationships of health, nutrition, physical fitness, and mental alertness and must strive to prevent any one of these components from achieving preeminence at the expense of another.

Essential to the success of any educational process is the availability of food, whether as meals or as foodstuffs, at prices which can be afforded by all—by individual consumers, or by government or nonprofit (quasi-government, since they pay no taxes) agencies who assume responsibility for low income consumers being fed at home or, in institutions, or by a combination of both.

The text of the recommendations of the Panel on Aging of the White House Conference on Food, Nutrition and Health appeared, in part, in the Final Report of the Conference released in April, 1970. Since the text of the recommendations of the Panel on Aging was incomplete because of accidental omissions during printing, an addendum containing the full text and the full listing of Panel members and consultants, also incomplete in the original text, was released in August, 1970. The full text included a Preamble and eleven recommendations. The complete text of the Preamble and summaries of the recommendations follow.

WHITE HOUSE CONFERENCE ON FOOD, NUTRITION AND HEALTH

SECTION II. NUTRITION OF VULNERABLE GROUPS

PANEL 4. THE AGING

Preamble

The present crisis among the aged demands immediate national action to relieve poverty, hunger, malnutrition, and poor health.

Furthermore, positive measures are required throughout life to retard the premature debilitating aspects of aging.

Certain priorities exist:

1. Provision of adequate income to the aging.
2. Provision of adequate nutrition to the aging.
3. Provision of adequate health services to the aging.
4. Federal, state and local funding to insure immediate implementation for (1), (2), and (3) above.
5. Prompt provision of substantial increases in federal funding for support of education, research, and development in nutrition and gerontology.

Recommendation I: Meal Delivery

The U. S. Government must now accept as an obligation the provision of the opportunity for adequate nutrition to every aged resident.

A new system of food delivery based on modern technology must be developed.

USAOA and USDA to implement a variety of meal delivery systems in the following ways:

1. A working party of experts to review experience with low-cost meals and meal delivery service and issue recommendations.

2. Government funding.
3. System of reimbursement with stamps, coupons, or credit cards.
4. Surveillance.

Recommendation II: Income

1. Social Security benefits to be increased by 50 per cent and the minimum benefit raised from $55 to $125 monthly within the next two years.
2. The public welfare system to be revised completely to provide payments based solely on need from federal funding and with federal administration.
3. The Federal Government to assure the distribution, availability and utilization of adequate information, facilities and services for maintaining and improving the nutrition and health of all Americans.
4. Federal Government to eliminate all barriers to adequate nutrition and health for all segments of the population, particularly those with special needs.
5. Social Security beneficiaries to receive income on parity with any implemented system of guaranteed annual income.

Recommendation III: Food Stamp Program Revisions

1. Prepared meals to be purchasable with stamps.
2. Eligibility to be established on the basis of self-declaration under federal standards.
3. Food stamps to be available to low income families without cost. These families to be allowed to purchase stamps at various times throughout the month.
4. HEW to monitor and evaluate the effectiveness of the stamp program.

Recommendation IV: Education, Research and Development

1. The Federal Government to develop a nutrition education program aimed at the elderly, but also emphasizing adequate nutrition throughout life as a means of preventing the disabilities associated with premature aging.
2. Consultation by competent, qualified personnel including those specializing in diet counselling to be made available.
3. Funds to be provided to improve training programs in nutrition and gerontology.
4. Surveys of institutionalized and noninstitutionalized aged to be conducted.
5. A National Commission for Mental Health of the Aged to be established.
6. Substantial funds to be devoted to support basic and applied research.

Recommendation V: National Code of Standards

The Government to establish a national code of health, nutrition and personnel standards and to use its powers to encourage each state to adopt and enforce this code among all persons and agencies providing residential care or home health care for the aged.

Recommendation VI: Housing and Dining Facilities

1. Housing for the elderly to include meal services with proper nutrition.
2. This service to be extended to older people in the neighborhood.
3. HUD to include in its programs for the elderly one that responds to the needs of those who are not ill but whose frail constitution prevents them from shopping and preparing meals.
4. The Federal Government to fund the construction of neighborhood centers for the elderly.
5. HUD and AOA to work together to develop a closer relationship between housing design, construction and the services needed to produce a rewarding environment.

Recommendation VII: Transportation for the Aged

The Department of Transportation, HEW and HUD to seek ways to provide necessary transportation for those seeking to take advantage of nutrition, health and other services.

Recommendation VIII: Packaging and Labeling

1. An economical, nutritious, easily prepared, attractive and readily stored new food line to be developed.
2. Promotion of these new products to be accompanied by an education program directed at those seeking economical, high-quality nutrition.
3. These new products to be labelled in clearly visible print with their nutrient contents translated into proportions of daily allowances of the four basic food groups.
4. The Federal Government to launch an educational campaign against food faddism utilizing the new food line, the education programs and the proposed labelling system.

Recommendation IX: Soil Bank Utilization for Home Gardens

Soil bank legislation to be amended to entitle persons to raise foods for personal consumption on soil bank land.

Recommendation X: Funding

1. The President to support vigorously federal action to provide adequate funds for immediate and realistic implementation of all aforementioned recommendations.
2. Evaluation to insure efficient, effective utilization of funds to be incorporated into every program.

Recommendation XI: Implementation

1. Action implementing these recommendations to be initiated immediately.
2. The President to establish a mechanism giving leadership to their effective development and a continuing monitoring of progress on each recommendation.
3. The forthcoming White House Conference on Aging to include a review and evaluation of progress on each of these recommendations as part of the responsibilities of a Panel on Nutrition with the objective of providing recommendations for future action.

During the weeks prior to the Conference itself, preparatory conferences were held in various regions of the country and were sponsored by groups and agencies concerned with all problems in human nutrition in America. Since aging begins at least at conception and continues to death, these preparatory conferences placed great emphasis on nutrition and aging.

Subsequent to the December, 1969, White House Conference in Washington, workshops have been held throughout the country to galvanize support for all recommendations of the Conference and to plan national and regional efforts to bring about the most rapid implementation possible of the recommendations.

One such workshop was planned during the December conference and came to fruition under the aegis of the Administration on Aging of the Department of Health, Education, and Welfare in Washington on August 7 and 8, 1970. This workshop, attended by over 30 representatives of federal, state, and local governments, universities, and private industry was concerned primarily with the implementation of Recommendations I, IV, VI, and VIII of the Panel on Aging.

The workshop concluded by drawing up a series of action steps to be catalyzed by the Administration on Aging to lead to implementation of these recommendations. In regard to Recommendation VIII, the work-

shop recommended: (1) collaboration with the NRC-NAS Food and Nutrition Board to establish standards for a new food line, including specifications as to the variety and type of foods to be included; (2) an investigation of legal requirements, practicality and acceptability of a labeling system which would complement efforts in nutrition education; (3) an industry-wide survey of existing products already nutritionally outstanding or which might be upgraded to meet the new product line specifications; this survey would include collection of data on present costs and future costs in anticipation of higher quality and packaging specifications and potential economics of scale; (4) a determination of quality control methods and of the agency to be responsible for exercising such control; (5) development of educational material to be used in promoting the new food line with emphasis of combating food faddism; (6) utilization of every possible method of reducing net cost to the consumer, including public service promotion if indicated; (7) test marketing and reevaluation during test marketing to assure the practicality of and wide utilization of the new product line.

In regard to Recommendation I, the workshop recommended: (1) the tailoring of specific meal delivery programs to local, ethnic, and cultural needs; (2) establishment of standards and specifications based on the NRC allowances but cast in practical terms for local implementation; (3) provision, when feasible, of meals in a social setting, while at the same time guaranteeing delivery of meals to those who of necessity are homebound; (4) flexibility in the options for meal purchase open to the consumer; (5) nutrition education as a part of every meal delivery scheme; (6) federal legislation to provide public funding for development of a nationwide meal delivery program; (7) meals to be provided 365 days a year, including weekends and holidays; (8) evaluation of costs, both unit and overall; (9) consideration of meal delivery to rural isolates, e.g., by utilizing the postal service.

In regard to Recommendation VI, the workshop proposed: (1) use of facilities and staff of new housing developments in behalf of those not in residence but living in the neighborhood; (2) enlargement of preparation and dining facilities in existing projects to include adequate facilities to accomodate tenants plus neighborhood residents; (3) sponsors of housing should be encouraged to put emphasis on the importance of nutrition to the consumers in the development of all housing plans; (4) provision should be made for central meal service in low rent public housing as well as in higher income and middle income federally supported housing programs where meal service is now provided; (5) legislation authorizing a subsidy or use of residual receipts should be passed so that all public housing provide at least one meal daily and that acceptance of this meal should be a requirement for occupancy; (6) HUD should conduct a management survey of existing projects providing meal service including an evaluation of the availability of catered meals to ascertain the most efficient, effective, and economical methods of supplying adequate nutrition; (7) HUD should collaborate with HEW in nutrition and all other programs where there is mutual advantage to be gained in specific areas of consumer need; (8) a dietitian should be

responsible for supervision of all meal planning and preparation and for diet counselling in public housing projects; (9) means tests should be eliminated, and housing with meal service should be made available solely on the basis of need; (10) as an interim measure, utilization of food stamps for the purchase of prepared meals as well as items for food preparation should be authorized.

In regard to Recommendation IV, the workshop proposed the following: (1) nutrition education for the elderly begins in infancy and needs to be continued throughout all years of education and later; (2) nutrition educational efforts must be directed at teachers of all levels and especially at policymakers in education and in government; (3) manpower needs to be developed for the purpose of working with those already in middle and old age to further diet counselling, basic nutrition education, and consumer buying practices; (4) elderly persons should be recruited to serve as nutrition aides to help teach nutrition to preschool and school children, and in so doing to learn and practice good nutrition for themselves; (5) nutrition education is to be incorporated into instruction given recruits and more seasoned personnel in the armed forces, and the armed forces food ration is to be tailored to individual needs to provide an example of appropriate nutrition; (6) nutrition education should be incorporated into all forms of pre-retirement counselling; (7) malnutrition secondary to primary disease must be emphasized in all nutrition education and especially among the elderly where morbidity rates are higher than among the rest of the population; (8) physical fitness and mental alertness need emphasis as being essential to maintenance of adequate nutritional status.

While the Administration on Aging was the first federal agency to organize a workshop to develop action steps to implement the recommendations of the White House Conference on Food, Nutrition, and Health, all federal departments and independent agencies have been under orders from the White House to review the recommendations, to develop proposals for implementation, and to estimate the costs involved. The USDA has already authorized major liberalizations in the Food Stamp Program. These moves have increased substantially the level of benefits to the poor and have dramatically increased (almost doubled) participation. The Congress is now considering a series of Administration-sponsored amendments to the Food Stamp Act, which would authorize eligible elderly to use their stamps to continue to purchase food for home preparation or to purchase prepared meals delivered to their homes by public or nonprofit private agencies. The Veterans Administration has proposed utilizing its facilities for food preparation and the food and nutrition expertise of its personnel in assisting the USDA, HEW, and OEO in meeting the nutritional needs of children and of the elderly within 200 miles of each VA hospital.

In December, 1970, a follow-up meeting sponsored by the White House will be held in Washington to be attended by Panel Chairmen and Vice Chairmen, among others, to review department and agency plans for implementation of the recommendations of the White House Conference on Food, Nutrition, and Health. Present also will be the news media and the representatives of consumer groups, including the

elderly, and professional societies who played such important roles in generating Conference recommendations. This unprecedented situation virtually demands a demonstration of positive action by every department and agency.

In the fall of 1971, the White House Conference on Aging will convene. Already included are plans for organization of a Panel on Nutrition. This Panel already has the assignment of making a critical review of all action steps recommended by the Panel on Aging of the White House Conference on Food, Nutrition and Health. This Conference too will be held in the glare of national publicity, insuring serious efforts on the part of all federal departments and agencies to produce evidence of true progress.

This presentation has summarized current thinking and recent action in regard to nutrition and aging. Details supporting this summary and providing the background cogent to recent actions may be found elsewhere.[2-7] An excellent review of the social, psychological, and economic aspects of nutrition and aging is also available.[2] The final report and its addendum of the White House conference on Food, Nutrition, and Health[8] is required reading for any serious student of the total problem.

Nutrition, like gerontology, is a program area for service, research, and teaching which involves all medical specialties and all of the basic behavioral, social, and political sciences. When nutrition and gerontology are viewed together, the breadth, scope, and depth of the problems become immense. Society is now tuned more than at any time in recent decades to meet the challenge of these program areas. This may well be the first epoch of true progress toward the elimination of malnutrition and, pari passu, premature biological aging, disability and death.

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ADDITIONAL ARTICLE

Treatment of Hyperlipidemic States*

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The Framingham[11] and other[5, 12] important prospective studies have clearly established hypertension and hyperlipidemic states as major (but not exclusive) risk factors in determining the statistical probability of development of overt manifestations of coronary heart disease. Blood pressure and serum cholesterol concentrations are continuous variables, so that a systolic blood pressure of 120 mm. Hg or lower is associated with a risk of developing coronary heart disease that is 3.8 times lower than the risk associated with a "normal" systolic pressure between 120 and 139 mm. Hg; similarly, a "normal" cholesterol level of 240 mg. per 100 ml. is associated with a risk in 30 to 49 year old men that is 2.6 times greater than that associated with a level of 200 mg. per 100 ml. These are now well-established facts, backed by thousands of man-years of experience gathered in several independent prospective studies. It is worth noting that blood pressure and blood lipid levels are multiplicative and synergistic risk factors; from this fact it follows that a patient whose hypercholesterolemia is refractory to treatment by diet and chemotherapy should be treated energetically to lower his blood pressure in order to minimize his over-all risk of developing coronary heart disease. Conversely, a hypertensive patient whose blood pressure is difficult to control deserves special effort directed toward reduction of his blood lipid levels. This important point having been made, the remainder of this discussion will deal with the diagnosis and management of hyperlipidemic states.

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The mere statistical association of hyperlipidemic states with increased incidence of coronary heart disease does not necessarily prove the causal involvement of a lipid factor in the pathogenesis of this disease. However, a large body of independent evidence based on animal experimentation leaves no doubt about the causal role of hypercholesterolemia in the experimental induction of atherosclerosis in practically every species studied (rat, chicken, rabbit, guinea pig, dog, monkey).[27, 30] Furthermore, regression of atherosclerosis occurs when the hypercholesterolemia is brought under control by diet or chemotherapy or both.[1, 23]

In man, two major studies, one American[3] and one Finnish,[31] have shown that diet therapy is successful in reducing mortality from coronary heart disease in healthy middle-aged male subjects in whom the prevalence of risk factors is increased ("primary prevention"). The National Diet Heart Feasibility study led to the same conclusion. Still further support for the value of a prudent type of diet (which again resulted in a small reduction in blood cholesterol concentrations) was provided by a large cooperative Veterans' Administration study which included some subjects with overt coronary artery disease.[4]

Four American studies[2, 21, 22, 24] and one carefully executed recent Norwegian study[16] have shown that the incidence rate of recurrent myocardial infarction (and deaths associated with infarction) is significantly lowered in diet-treated subjects compared to matched control subjects. On the other hand, two English studies[20, 26] have failed to confirm the benefit of diet therapy in middle-aged men who had sustained one myocardial infarction. Nevertheless, the preponderance of evidence definitely supports the value of a blood lipid-lowering diet in reducing coronary heart disease in middle-aged, overtly healthy men, as well as in those individuals who have already had one myocardial infarction. Parenthetically it might be noted that these studies do not indicate the detailed mechanism by which diet exerted its beneficial effect; e.g., a direct effect in reversing atherosclerosis, or an effect on the coagulation mechanism, etc.

Whereas diet therapy is undoubtedly of value in populations with a high prevalence of risk factors, an even more urgent problem is presented by patients who have a familial, acquired, or environmentally determined hyperlipoproteinemia. Even though appropriate diet therapy should be used in these individuals (as will be described in more detail below), a sizable percentage of such individuals fail to respond to diet therapy, are unable to maintain their diet, or for various reasons eventually escape dietary control of their hyperlipoproteinemia. For these individuals appropriate chemotherapy is clearly indicated, and is most likely to be of even greater value than diet therapy in the general population, in whom blood lipid concentrations are usually considerably lower. This hypothesis has not yet been proved but is under current study in various drug trials in this country and abroad. An excellent discussion stressing the need for an organized preventive medical approach to the problem of atherosclerosis has appeared recently.[10]

In short, a large body of evidence clearly indicates that high blood lipid levels are causally related to coronary heart disease and that their

modification by diet is of distinct benefit; it is very likely that effective chemotherapy in patients with greatly elevated lipid levels found in hereditary and acquired types of hyperlipoproteinemias is of even greater potential benefit. This is the rationale for the chemotherapy of hyperlipidemic states discussed below.

CLASSIFICATION OF HYPERLIPOPROTEINEMIAS

Treatment of the various hyperlipoproteinemic states is best and most rationally carried out only after the most accurate and careful diagnosis has been made of the particular hyperlipoproteinemia exhibited by the patient. The most widely available and most practicable method of classification is that devised by Lees and Hatch[15] and applied by Fredrickson and associates,[6] based on the appearance of lipoprotein (LP) bands following paper electrophoresis; this classification is shown in Table 1.

An even simpler method of classification of hyperlipidemic states is based on the appearance of serum kept overnight in a refrigerator at 4° C. If the serum is clear (usually amber-colored), the only hyperlipoproteinemia that can be present is Type II, which is easily confirmed by the finding of a high cholesterol concentration but a normal, subnormal, or only slightly elevated triglyceride level. If the serum has a distinct, creamy top layer, the presence of chylomicrons can be inferred; if the infranatant layer is clear, one may diagnose Type I disease (a very rare primary hyperchylomicronemia); but if the infranatant layer is uniformly turbid or milky, one may infer the presence of large quantities of prebetalipoprotein, which leads to a diagnosis of Type V disease. The serum in Type III and Type IV disease is usually uniformly turbid or milky, but without a distinct creamy top layer; occasionally, moderate concentrations of chylomicrons may be present in Type IV disease, and the paper electrophoretogram may then be interpreted as Type V. Types III and IV cannot be distinguished by inspection of the serum or by paper electrophoresis alone; a separate preparative ultracentrifugal step is necessary to show the presence of a betalipoprotein with abnormally low density, causing it to float at density 1.006. An accurate and quantitative diagnosis can also be made by analytic ultracentrifugation. Without ultracentrifugal steps, but with paper electrophoresis combined with cholesterol and triglyceride determinations, a presumptive diagnosis of Type III can be made with relatively high cholesterol concentrations (cholesterol/triglyceride ratio greater than 1) and of Type IV if this ratio is below 0.8. Table 3 lists important clinical features, some having practical diagnostic value, of the various types of hyperlipoproteinemias.

Paper electrophoresis combined with cholesterol and triglyceride determinations is adequate for all clinical purposes, including follow-up of the effect of diet and chemotherapy in most hyperlipidemias. Analytic ultracentrifugation, recently refined by addition of computerized techniques, allows an extremely detailed and quantitative analysis of the

Table 1. *Classification of Hyperlipoproteinemias by Paper Electrophoresis*

TYPE	APPEARANCE OF SERUM	CHYLOMICRONS	β-LIPOPROTEINS	PRE-β-LIPOPROTEINS	α-LIPOPROTEINS	SERUM CHOLESTEROL CONCENTRATION	SERUM TRIGLYCERIDE CONCENTRATION
I	Creamy	Medium*	Light	Light	Light	Low to average	Very high
II	Clear	Absent	Dark, narrow	Absent, light, or medium	Light	Very high	Usually low to average, occasionally slightly increased
III	Turbid	Usually absent	Medium, wide	Not separated from β band	Light	High to very high	High
IV	Turbid	Absent, light, or medium	Light	Medium or dark, usually wide	Light	Normal to high	High to very high
V	Creamy or turbid	Medium	Light	Medium or dark, usually wide	Light	High	Very high

*Absent, light, medium, and dark describe the intensity of color of stain of the specific lipoprotein band.

Table 2. *Some Properties of Lipoproteins*

LIPOPROTEIN (LP)	SF RATE	DENSITY	ELECTROPHORETIC MIGRATION RATE	PARTICLE SIZE Å RANGE	APPROXIMATE CHEMICAL COMPOSITION (%)			
					Protein	Cholesterol Total	Triglyceride	Phospholipid
	Sediments at							
High density LP (HDL)	1.063	1.063–1.20	α_1	65– 95	45	25	5	25
Low density LP (LDL)	0–20	1.006–1.063	β	200– 250	20	50	5	25
Very low density LP (VLDL)	20–400	0.96 –1.006	Pre β	250– 800	10	15	60	15
Chylomicrons	> 400	< 0.96	Remains at origin	800–5000	1	4	90	5

Table 3. *Clinical Features of Hyperlipoproteinemias*

TYPE	TYPICAL XANTHOMAS AND LIPID STIGMATA	ASSOCIATED DISEASES CLINICAL FINDINGS	OTHER DISEASES CAUSING SIMILAR LIPOPROTEIN PATTERN
I Familial hyperchylomicronemia Fat-induced hyperlipemia	Occasional eruptive	Periodic acute abdominal pain	Excessive fat consumption Severe insulin-dependent diabetes, poorly controlled
II Essential, familial hypercholesterolemia Xanthoma tendinosum with Sf 0–12 hyperlipoproteinemia	Tendinous xanthomas Achilles tendon, patellar tendon, extensor tendons of fingers Arcus senilis Xanthelasma	Severe atherosclerosis Often thin and tall	Hypothyroidism High dietary cholesterol intake
III "Broad β"	Cutaneous tuberous xanthomas over elbows, knees, buttocks, creases of fingers	Atherosclerosis Obesity Hyperuricemia	None
IV Pre β hyperlipoproteinemia Sf 20–400 hyperlipoproteinemia Carbohydrate-induced hyperlipemia	Eruptive xanthomas of trunk and extremities Lipemia retinalis	Atherosclerosis Hyperuricemia Obesity Diabetes Pancreatitis	Severe diabetes mellitus, poorly controlled
V Familial combined fat and carbohydrate inducible hyperlipemia	Eruptive xanthomas Lipemia retinalis	Atherosclerosis Abdominal pain Obesity Diabetes or decreased glucose tolerance	Diabetes mellitus, poorly controlled Alcoholism

entire lipoprotein spectrum, in which 29 low density and 15 high density fractions can be measured.[19] This method is complex and time-consuming and is therefore used chiefly for research purposes. In the present report, all four of the major low density lipoprotein (LDL) and the two important high density lipoprotein (HDL) ultracentrifugal classes will be discussed and correlated with electrophoretic paper strip analysis. Table 2 lists some common properties of lipoproteins as defined by ultracentrifugation, paper electrophoresis, and chemical analysis, and shows a comparison of electrophoretic and ultracentrifugal terminology. A recent detailed comparison of ultracentrifugal and paper electrophoretic techniques is available.[7]

GENERAL PRINCIPLES IN THE TREATMENT OF HYPERLIPIDEMIAS

Chylomicronemias (Types I and V) represent the accumulation of very large lipoprotein molecules derived from exogenous dietary fat. These disorders are probably due to a defect, or temporary inhibition, of the enzyme system lipoprotein lipase, which is necessary for the normal cellular utilization of chylomicrons. It is therefore easy to understand and to remember that treatment consists simply of drastic reduction in dietary fat intake; deficient fat intake can be supplemented with medium chain triglycerides[9] to augment total caloric intake if necessary. Medium chain triglycerides are commercially available as a powdered product (Portagen, Mead Johnson Laboratories). The fatty acids in this triglyceride preparation have 8 and 10 carbon atoms (75 per cent octanoic and 25 per cent decanoic acid), and are absorbed directly into the portal circulation, thus bypassing the intermediate transport stage of chylomicron formation which precedes tissue utilization.

Hypertriglyceridemias are a manifestation of the presence of excessive concentrations of Sf 20-400 or very low density lipoproteins (VLDL) in plasma. These species are smaller than chylomicrons but are large enough to scatter light effectively and therefore impart to the plasma a uniformly turbid to milky appearance when they are present in high concentrations. Very low density lipoproteins are synthesized in the liver from carbohydrate precursors and are termed *endogenous particles*. It is therefore rational that restriction of the dietary intake of carbohydrate is the mainstay of the treatment of hypertriglyceridemic states, namely, Types III, IV, and V. Weight reduction is usually observed on diets adequately restricted in carbohydrate, but control of obesity may also be of independent benefit.

Essential familial hypercholesterolemia (Type II of Fredrickson), especially when associated with tendon xanthomatosis, is generally refractory to dietary treatment. But in (presumably heterozygous Type II) patients without xanthomatosis, and with lower mean betalipoprotein concentrations, dietary restriction of saturated fats and of cholesterol is sometimes effective, particularly if the diet was high in cholesterol content. However, by far the greatest number of treatment failures occur in Type II patients.

Because dietary treatment is safer and more physiological than any form of chemotherapy (except for treatment directed toward the underlying disease in secondary forms of hyperlipoproteinemias; i.e., thyroid hormone in hypothyroid states), diet should always be given a careful trial before any form of chemotherapy is contemplated. As a general rule, chemotherapy is indicated only if diet treatment has failed or partially failed, is unacceptable to the patient, or loses efficacy over a period of time (months to years), presumably because the patient slowly relaxes his dietary restrictions.

SPECIFIC GUIDELINES FOR CHEMOTHERAPY

Chylomicronemias usually do not respond to chemotherapy; therefore, Type I should be treated only with a low fat diet, and Type V with a low fat, low carbohydrate diet; this is equivalent to the usual weight reducing low caloric diet. CPIB (Atromid-S) may also be effective in partially normalizing the lipoprotein distribution in Type V disease.

In Type II disease, without tendon xanthomatosis, with no family history of hypercholesterolemia, with cholesterol levels below 400 mg. per 100 ml., and Sf 0-20 lipoprotein concentrations below 900 mg. per 100 ml., CPIB will usually produce a 20 to 25 per cent reduction in low density lipoprotein concentration. This drug should therefore be tried first, as it is easier to use than other agents. Figure 1 illustrates the response of a typical patient with (probably heterozygous) Type II disease

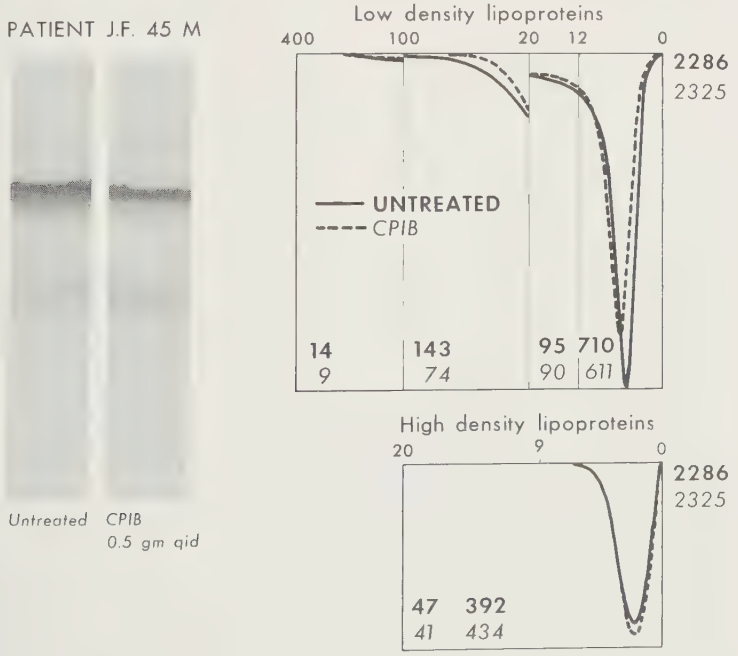

Figure 1. Effect of CPIB (Atromid S) in a 45 year old man with Type II hyperlipoproteinemia without xanthomatosis.

to CPIB, as seen with paper electrophoresis and analytic ultracentrifugation. If CPIB is ineffective, thyroid hormone should be used next, in increasing dosage as needed, or to tolerance. In our experience, doses of 4 to 6 grains are well tolerated by the majority of these subjects, provided that they do not have symptomatic ischemic heart disease. A 20 to 30 per cent reduction in cholesterol concentration can often be achieved by thyroid-active substances, but complete normalization of the lipoprotein pattern is seldom, if ever, possible. Figure 2 illustrates the effect of dried thyroid in a patient in this group.

In Type II disease associated with xanthomatosis and/or with very high Sf 0-20 concentrations, much higher doses of thyroid are required, ranging up to the equivalent of 12 or even 15 grains of dried thyroid. Even then, cholesterol or lipoprotein level reductions exceeding 20 to 30 per cent are difficult to accomplish. In persons with coronary heart disease, cautious use may be made of dextrothyroxine in increasing doses until either undesirable hypermetabolism occurs or the desired end is achieved. Usually, amounts exceeding 8 mg. per day are poorly tolerated, but exceptions do occur. The patient's reaction to thyroid-active substances is often dependent upon his physician's confidence and support; with experience, careful follow-up, and thorough knowledge of the actions of the hormone it is possible in 30 to 50 per cent of patients to achieve high dosage levels without significant tachycardia; the only common systemic effect is some weight loss, which is often beneficial and appreciated by the patient.

When thyroid-active substances are not effective or are poorly tolerated, nicotinic acid may be tried next, beginning with 1.5 to 2.0 gm.

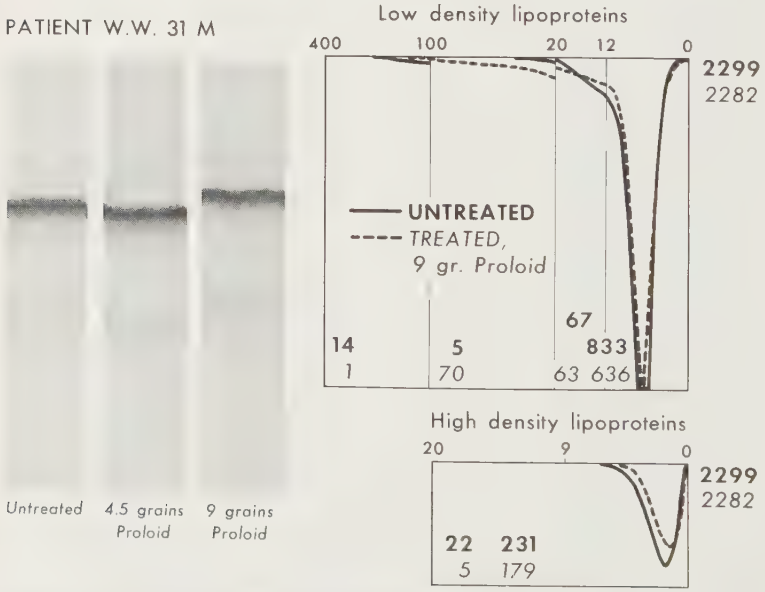

Figure 2. Effect of thyroid-active substance in a 31 year old man with Type II hyperlipoproteinemia without xanthomatosis.

daily and increasing to 3.0 to 4.5 gm. daily. Activation of peptic ulcer, abnormalities of liver function, and exacerbation of diabetes are all possible untoward effects, but with careful monitoring do not necessarily interdict use of the drug if it is effective and tolerated by the patient, without such complications. It is the only drug which, in my experience, has reduced betalipoprotein concentrations to a significantly greater degree than large doses of thyroid-active substances. Nicotinic acid has been used for many years by Parsons, and his reports[25] should be studied before one embarks upon long-term use of nicotinic acid.

Hyperprebetalipoproteinemias (Types III and IV) are frequently well treated with CPIB (Atromid-S). However, in Type IV disease, the effect of CPIB should be monitored with serial paper electrophoretic strips to allow a careful comparison of the intensity of the beta band. If the intensity of this band increases, an undesirable lipoprotein shift has taken place and CPIB should be stopped. Ultracentrifugal studies have shown that severe forms of Type IV disorders frequently respond to CPIB with a marked increase in the betalipoprotein concentration;[28, 29] this may be considered equivalent to the iatrogenic conversion of a Type IV to a Type II disorder. Since Type II disorders are the most malignant disturbances in terms of association with severe coronary atherosclerosis, the substitution of a Type II disturbance for a Type IV disorder is most likely deleterious to the patient. The Type IV to Type II lipoprotein shift is generally unimportant if the Type IV disturbance is mild or moderate (triglyceride concentration less than 350 mg. per 100 ml.); if it is severe (triglyceride concentration greater than 500 mg. per 100 ml.), a significant shift occurs in nearly all cases. Figure 3 illustrates the beneficial effect of a low carbohydrate diet (150 gm. carbohydrate per day for several months) in a patient with Type IV disease. The analytic ultracentrifugal analysis reveals an insignificant increase in Sf 0-20 concentrations, accompanied by a profound reduction in Sf 20-100 (from 549 to 161 mg. per 100 ml.) and Sf 100-400 (from 977 to 101 mg. per 100 ml.) levels; in addition, chylomicron concentrations* decreased from 660 to 53 mg. per 100 ml. No significant changes occurred in the high density lipoprotein levels.

Type III disease responds very well to CPIB and no untoward lipoprotein shift occurs in this disorder, as is well illustrated by the example shown in Figure 4. Noteworthy is the reduction in intensity of the "broad-beta" band and the dramatic reduction in lipoprotein concentration in the Sf 20-100 (from 907 to 311 mg. per 100 ml.) and Sf 100-400 (from 420 to 50 mg. per 100 ml.) classes. It also shows the usual increase in high density lipoprotein concentration (HDL_3 rose from 210 to 319 mg. per 100 ml.) produced by CPIB. The ultracentrifugal characteristics of Type III disease were described by Gofman et al. in 1951;[8] they consist of

*Ultracentrifugal measurement of lipoprotein concentrations above Sf rate 400 (representing chiefly chylomicrons or chylomicron-like particles) probably represent a measure of the minimum quantity of chylomicrons actually present; i.e., other methods of measurement may yield higher but not lower concentrations of these particles.

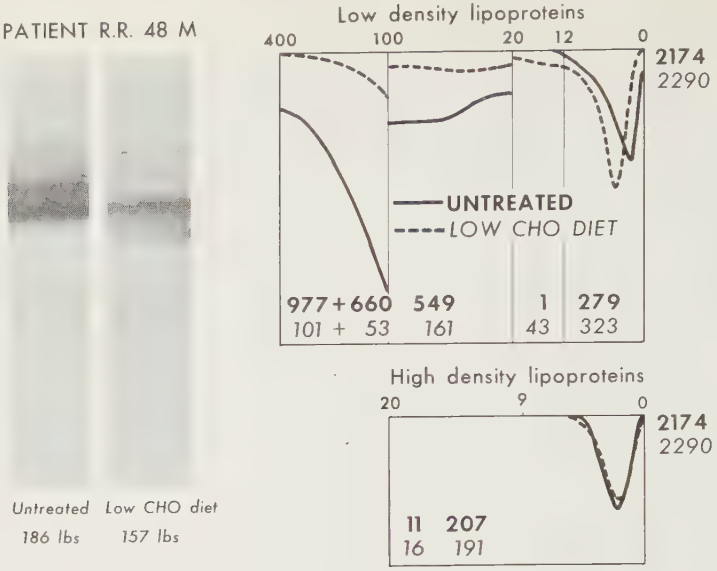

Figure 3. Effect of low carbohydrate diet in a 48 year old man with Type IV hyperlipoproteinemia.

low Sf 0-12 and high Sf 12-20, Sf 20-100, and Sf 100-400 concentrations. In most cases, Sf 20-100 are considerably higher than Sf 100-400 concentrations. Figure 4 illustrates these relationships. Type III is, therefore, the ideal indication for the use of CPIB.

Table 4 summarizes diet and drug treatment of the five types of hyperlipoproteinemias as discussed above.

Before embarking upon treatment with any particular drug, it is desirable to have some idea of the probability that the drug will work and just how effective it is likely to be. These criteria may be thought of as the *efficacy* of the drug, and are listed in Table 5 for CPIB, levothyroxine, and dextrothyroxine. The table lists the effect of each of these drugs on the major hyperlipoproteinemias as observed by the authors in more than 5 years' experience in treating patients with lipid disorders. The data are taken from a recent review[29] and have been summarized for this report.

Perusal of Table 5 shows that it is essentially a quantitative elaboration of the recommendations for treatment contained in Table 4; in addition it illustrates the following points: (1) Group 1 patients (Fredrickson Type II with xanthomatosis) respond to levothyroxine and dextrothyroxine but not to CPIB; the thyroid-active hormones have been effective in 100% of patients treated, but only a 20% reduction in Sf 0-20 (LDL) concentration can be expected, on the average. (2) In Group 2 patients (Fredrickson Type II without tendon xanthomatosis), all three agents appear to be effective, with low density lipoprotein reductions ranging approximately from 20 to 30 per cent; if Sf 20-400 (VLDL) con-

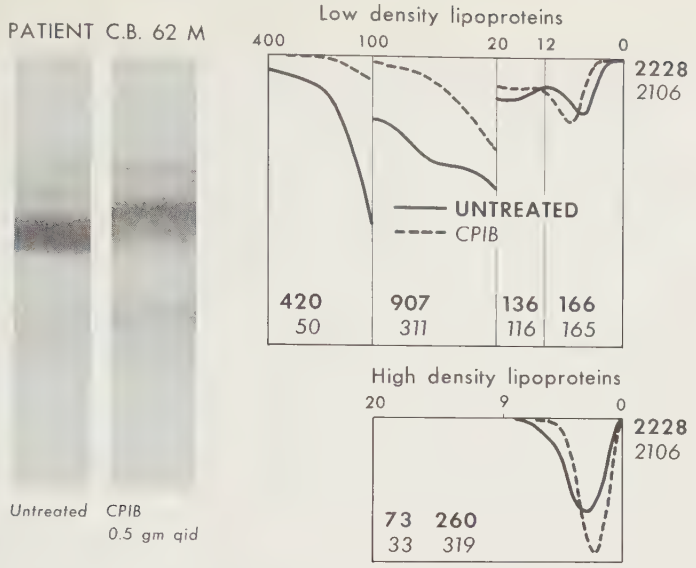

Figure 4. Effect of CPIB (Atromid S) in a 62 year old man with Type III hyperlipoproteinemia with xanthoma tuberosum.

Table 4. *Outline of Diet and Drug Treatment of Hyperlipoproteinemias*

TYPE	DIET	CHEMOTHERAPY
I	Very low fat diet Medium chain triglycerides	None
II	*With xanthomatosis* Low cholesterol, low saturated fat, unsaturated fat supplements (i.e., 3 oz. corn oil)	Nicotinic acid Large doses of thyroid hormone Cholestyramine
	Without xanthomas Same	CPIB Thyroid hormone
III	Low carbohydrate diet (100–150 gm. per day) Weight reduction	CPIB
IV	Low carbohydrate diet (100–150 gm. per day) Weight reduction	CPIB (discontinue if chronic hyperbetalipoproteinemia results)
V	Low carbohydrate and low fat diet Weight reduction	CPIB?

Common dose ranges:
Nicotinic acid, 0.5 to 1.5 gm. t.i.d. p.c.
Dried thyroid 3 to 8 grains per day; levothyroxine 0.3 to 0.6 mg. per day; dextrothyroxine 4 to 10 mg. per day.
Cholestyramine 16 to 32 gm. per day.
CPIB (Atromid-S) 0.5 gm. t.i.d. p.c. and h.s. (2.0 gm. per day).

Table 5. *Efficacy of CPIB and Levothyroxine and Dextrothyroxine*

GROUP:* FREDRICKSON TYPE		CPIB (ATROMID-S)		LEVOTHYROXINE		DEXTROTHYROXINE	
		Sf 0–20	Sf 20–400	Sf 0–20	Sf 20–400	Sf 0–20	Sf 20–400
Group 1	Initial concentration (mg. per 100 ml.)†	932	165	983	71	945	168
Type II	Change (%)†	−4	−35	−20	+4	−17	−23
	Fraction of group responding	5/8‡	7/8	7/7	2/7	6/6	5/6
Group 2	Initial concentration (mg. per 100 ml.)	786	127	746	101	808	147
Type II	Change (%)	−23	−47	−21	−5	−33	−9
	Fraction of group responding	12/12	11/12	14/14	5/14	6/6	1/6
Group 3	Initial concentration (mg. per 100 ml.)	359	1325				
Type III	Change (%)	+3	−71				
	Fraction of group responding	3/7	7/7				
Group 4	Initial concentration (mg. per 100 ml.)	393	1667				
Type IV, V	Change (%)	+59	−64				
	Fraction of group responding	11/11	11/11				
Group 5	Initial concentration (mg. per 100 ml.)	609	442	597	338	569	422
Type II	Change (%)	−1	−57	−7	−33	−25	−15
	Fraction of group responding	9/15	15/15	3/4	4/4	4/4	3/4

*Group refers to a classification based on the absolute concentrations of lipoproteins in Sf 0–20 (LDL) and Sf 20–400 (VLDL) classes. (See explanation in text.)

†Mean group values.

‡5/8 Indicates that five of a total of eight patients comprising this group responded to CPIB with decreases in Sf 0–20 concentrations.

centrations are also increased, CPIB would be the agent of choice, as it reliably reduces this fraction by about 50 per cent. (3) In Group 3 patients (Fredrickson Type III), CPIB is uniformly and almost amazingly effective; VLDL reductions averaging 70 per cent can be expected. (4) In Group 4 patients (Fredrickson Type IV and V), CPIB is also 100 per cent effective (major VLDL reductions having been observed in all 11 patients treated) in reducing VLDL concentrations by an average of 64 per cent; however, in all patients so treated, Sf 0-20 (LDL) concentrations increased, on the average by 59 per cent; in some patients increases up to 140 per cent have been observed. If this lipoprotein shift results in Sf 0-20 concentrations significantly above normal levels, thus inducing an iatrogenic Type II pattern, the drug should be discontinued, as has been noted above. (5) In Group 5 patients (Type II of Fredrickson), only thyroid-active substances appeared effective in reducing Sf 0-20 concentrations; CPIB lowered LDL concentrations in only nine of 15 patients and caused an increase in the remaining six, so that the group concentration change was only −1 per cent. (6) Table 5 demonstrates clearly the great efficacy of CPIB as a VLDL-lowering agent, regardless of the type of hyperlipoproteinemia.

Perhaps the most important of all aspects of chemotherapy concerns the nature, severity, and frequency of side effects which may be expected. My experience in this area is summarized in Table 6, which lists the side effects observed in 78 patients receiving CPIB and in 76 patients during treatment with various thyroid-active agents; since many patients were receiving these drugs serially at one or another time during prolonged periods of observation, the number of patients studied totaled 107.

Because of the difficulty of defining exactly what constitutes a "side reaction," and to allow as direct a comparison as possible between CPIB and thyroid-active substances, all untoward events that occurred during treatment with these drugs were recorded. It is likely that myocardial infarction in the middle-aged, high-risk group studied would have occurred with comparable frequency without any chemotherapy, so that this event is probably not attributable to the chemotherapeutic agent in question; indeed, Table 6 does suggest strongly that the incidence of infarction in the CPIB and thyroid-hormone treated group was the same. Therefore one may reasonably assume that neither drug had a significant effect in promoting infarction. On the other hand, chest pain occurred approximately three times as frequently in the group treated with thyroid-active substances and therefore most likely constitutes an effect attributable to these agents. Gastrointestinal symptoms of minor nature have frequently been reported to be associated with CPIB therapy, and were again observed in the present group; muscle aches have also been reported to be associated with this drug[11] and appear clearly more common than in the thyroid-treated group, while tremors and nervousness were found in patients taking thyroid-active substances. Since the study was not blind, it is very likely that considerable bias on the author's part (in expecting just such reactions, particularly at higher dose levels) contributed to the relatively high incidence recorded in Table 6. In general, the data indicate that chest pain and hypermetabolic reactions are com-

Table 6. *Comparison of Side Effects Observed with CPIB and Thyroid Active Substances*

SIDE EFFECT	CPIB (78 PATIENTS)		THYROID ACTIVE SUBSTANCES (76 PATIENTS)	
	No.	%	No.	%
Myocardial infarction during treatment and within 4 weeks post treatment	6	8	5	6.3
Chest pain	4	5	12	16
Gastrointestinal symptoms	6	8	2	2.6
Muscle aches	4	5	1	1.3
Tremor, nervousness	0	0	20	26
Other reactions	12	15	0	0
Total		41		52
Cardiovascular reactions (myocardial infarction, chest pain)		13		22
"Hypermetabolic" reactions		0		26

mon side effects in patients receiving thyroid-active substances, while minor gastrointestinal symptoms and a variety of other reactions appear more commonly associated with CPIB.

Pertinent to this review are the following recent articles: the excellent paper on electrophoretic diagnosis and on management of hyperlipoproteinemia by Levy and Fredrickson,[17] and Levy and Glueck's lucid discussion of the relationship of hypertriglyceridemia to diabetes mellitus and coronary artery disease,[18] a discussion of the treatment of a large group of hyperglyceridemic patients by Kuo,[13] and Wessler and Avioli's concise review of the classification and treatment of hyperlipoproteinemias.[32]

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7. Owner: Atwell & Company, 45 Wall St., New York, N.Y. 10005; Anderson & Company, 135 S. Broad St., Philadelphia, Pa. 19109; Bark & Company, P. O. Box 351, Boston, Mass. 02101; Barnett & Company, 16 Wall St., New York, N.Y. 10015; Cede & Company, Box 20, Bowling Green Sta., New York, N.Y. 10004; Cudd & Company, One Chase Manhattan Plaza, New York, N.Y. 10015; Firjer & Company, One Exchange Place, Jersey City, N.J. 07303; Kane & Company, One Chase Manhattan Plaza, New York, N.Y. 10015; King & Company, 399 Park Ave., New York, N.Y. 10022; Arthur Judson & Company, Room 820, 12 S. 12th St., Phila., Pa. 19107; Leon Levy, 123 S. Broad St., Philadelphia, Pa. 19109; Lerche & Company, 48 Wall St., New York, N.Y. 10015; William S. Paley, 51 West 52 St., New York, N.Y. 10019; Peak & Company, P.O. Box 351, Boston, Mass. 02101; Frank Stanton, 51 West 52 St., New York, N.Y. 10019; Stuart & Company, 399 Park Ave., New York, N.Y. 10022.
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9. Paragraphs 7 and 8 include, in cases in which the stockholder or security holder appears upon the books of the company as a trustee or in any other fiduciary relation, the name of the person or corporation for whom such trustee is acting. Also the statements in the two paragraphs show the affiant's full knowledge and belief as to the circumstances and conditions under which stockholders and security holders who do not appear upon the books of the company as trustees hold stock and securities in a capacity other than that of a bona fide owner. Names and addresses of individuals who are stockholders of a corporation which itself is a stockholder or holder of bonds, mortgages, or other securities of the publishing corporation have been included in paragraphs 7 and 8 when the interests of such individuals are equivalent to 1 per cent or more of the total amount of the stock or securities of the publishing corporation.
10.

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B. Paid circulation		
1. Sales through dealers and carriers, street vendors, and counter sales	———	———
2. Mail subscriptions	35,208	35,633
C. Total paid circulation	35,208	35,633
D. Free distribution (including samples) by mail, carrier, or other means	200	200
E. Total distribution (sum of C and D)	35,408	35,833
F. Office use, left-over, unaccounted, spoiled after printing	3,492	2,367
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I certify that the statements made by me above are correct and complete.

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